

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

Date: November 18, 2008

Re: Vorinostat

Dear Doctor:

This letter is to provide follow-up information on an adverse experience concerning Vorinostat 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 # 0805USA05040, GENSTUDY # 055-0007, AN # 1799

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 0805USA05040
UF/Dist report #	
	FDA Use On

A. Patient information			
1. Patient identifier Unk AN 1799 in confidence	2. Age at time of event: or 78 years Date of Birth: 04/30/1930	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 213 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)	05/20/2008	4. Date of this report (mm/dd/yyyy)	11/18/2008
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5. Describe event or problem
This is in follow-up to report(s) previously submitted on 7/31/2008; 8/11/2008; 8/22/2008; 10/31/2008; 11/7/2008; 11/14/2008

A Phase I Clinical Trial of Vorinostat in Combination With Decitabine in Patients With Acute Myelogenous Leukemia or Myelodysplastic Syndrome

Information has been received from an investigator concerning a 78 year old male with congestive heart failure, benign prostatic hypertrophy, on anticoagulant therapy, hypertension, coronary artery disease, pain, groin infection, type 2 diabetes mellitus, groin abscess, anxiety, vascular imaging, hypokalaemia, insomnia, atrial fibrillation, cholelithiasis, dyspnoea, oedema lower limb, fatigue, hearing loss, arthroscopy left knee, left ventricular dilatation, q axis, left axis deviation, dilatation atrial, non-specific ST & T wave abnormality ("probably digitalin effect"), polymyalgia rheumatica, bilateral pleural effusions, urinary retention, vertebral disc operation, shoulder pain and hypokinesia and a

(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: Coronary artery bypass graft; Human ehrlichiosis; Postoperative wound infection; Inguinal hernia repair; Sinusitis; Inguinal hernia; Staphylococcal infection
CONCURRENT CONDITIONS: Benign prostatic hypertrophy; Hypertension; Coronary artery disease; Postoperative infection; Pain;

(Continued on Additional Page)

C. Suspect medication(s)	
1. Name (Give labeled strength & mfr/labeler)	
# 1	CAP vorinostat 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 03/31/2008 - 04/13/2008
# 2	# 2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced.
# 1 Acute myelocytic leukaemia	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	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	# 2	# 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)	
ASPARTAT	07/23/2008-07/30/2008
AVELOX	07/16/2008-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
3. Report source. (check all that apply)	
<input 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	

4. Date received by manufacturer (mm/dd/yyyy)	5. (A)NDA # 21991 IND # 58915
11/03/2008	
6. If IND, protocol #	STN # PMA/ 510(k) #
0550007	
7. Type of report	Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC product <input type="checkbox"/> Yes
<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# 6	9. Mfr. report number WAES 0805USA05040

8. Adverse event term(s)
FEBRILE NEUTROPENIA; CELLULITIS; FEBRILE NEUTROPENIA;
MYOCARDIAL INFARCTION

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**

history of sinusitis, coronary artery bypass graft, human ehrlichiosis, postoperative wound infection, inguinal hernia repair for a left inguinal hernia, and staphylococcal infection of the upper lip who on 31-MAR-2008 was randomized and placed on cycle 1 therapy with vorinostat, capsule, 400 mg, once a day for acute myelocytic leukemia (Diagnosed 26-MAR-2008). Concomitant study therapy included decitabine 20 mg/m² (45mg), administered IV for 5 days, initiated on 31-MAR-2008. Other concomitant therapy included morniflumate (FLOMAX (morniflumate)), benazepril HCl (LOTENSIN), amlodipine besylate (NORVASC), digoxin, docusate Na (COLACE), oxycodone, pantoprazole sodium (PROTONIX), moxifloxacin hydrochloride, acyclovir, nystatin, lisinopril (manufacturer unknown), chlorhexidine gluconate, metformin, imaging, acetaminophen, diphenhydramine HCl, ondansetron hydrochloride (ZOFTRAN), prochlorperazine maleate (COMPAZINE), lorazepam, calcium carbonate (+) magnesium hydroxide (ROLAIDS), calcium carbonate (TUMS), vancomycin, piperacillin sodium (+) tazobactam sodium (ZOSYN), moxifloxacin hydrochloride (AVELOX), fluconazole (DIFLUCAN), acetylcysteine (MUCOMYST), sulfamethoxazole (+) trimethoprim (BACTRIM DS), mupirocin, chlorhexidine gluconate (HIBICLENS), carvedilol (COREG), clopidogrel bisulfate (PLAVIX), magnesium aspartate (+) potassium aspartate (ASPARTAT), rosuvastatin calcium (CRESTOR), labetalol. On 30-APR-2008 the patient was started on cycle 2 of study therapy and was completed on 13-MAY-2008.

On 20-MAY-2008 day 22 of cycle 2 the patient presented to the doctor's office with complaints of fever. The patient's temperature was 100.1 and 100.4 at home. Laboratory diagnostic studies included lymphocyte count 76, monocyte count 0, neutrophil count 4, white blood cell count 1.4. The patient complained of a boil on his groin which he reported to have for 2 to 3 weeks. The patient was admitted to the inpatient unit where he remained afebrile during the course of hospitalization. The pustule in the right groin was noted. The patient was noted to have groin cellulitis (grade 3). All cultures excluding the wound culture were negative. The wound culture showed an abundant growth of staph aureus, ethicillin resistant and there was a light growth enterococcus specie. The patient was treated with warm compresses on the groin and vancomycin during the hospital stay. The patient was instructed to continue at home. Vancomycin was discontinued at discharge. Discharge diagnosis was fever secondary to right groin cellulitis. The patient was to take linezolid 600 mg BID orally at home for 5 days. The patient returned to the clinic for an appointment on 28-MAY-2008 and recovered. Laboratory diagnostic studies included lymphocyte count 74, monocyte count 9, neutrophil count 12, white blood cell count 1.2. On 28-MAY-2008 the patient was started on cycle 3 study therapy and completed on 10-JUN-2008.

On 16-JUN-2008, the patient presented to the clinic with complaints of having a fever at home. He stated his temperature was 101.3 at home. Upon admission it was 100.8. The patient also complained of nausea and vomiting when he tried to eat that day as well as mild maxillary tenderness. On 16-JUN-2008 the patient experienced febrile neutropenia (grade 3). Blood and urine cultures were obtained as were a sinus and cat scan which showed opacification of the left mastoid air cells in the middle ear associated with tympanic membrane thickening suspicious for mastoiditis. It was reported that maxillary tenderness resolved by day 2. The patient was treated with imipenem which was discontinued upon discharge and the patient was put back on moxifloxacin hydrochloride (AVELOX) which he had been taking prophylactically prior to admission. The patient was afebrile and appearing clinically well upon discharge. A urine culture was positive for a minimal number of gram negative rods. On 20-JUN-2008, the patient was considered recovered from febrile neutropenia (grade 3) and was discharged. Discharge diagnosis was febrile neutropenia. The patient visited the clinic on 25-JUN-2008. On 25-JUN-2008 the patient was treated with ciprofloxacin hydrochloride (CIPRO) for epididymitis. On 02-JUL-2008, the patient was placed on cycle 4 of study therapy which was completed on 15-JUL-2008. On 09-JUL-2008 a grown biopsy showed an abundant growth of Staphylococcus aureus and was methicillin resistant.

On 21-JUL-2008, the patient presented to the inpatient unit with a complaint of generalized weakness and fever. The patient's temperature was reported to be 101.4 at home orally. The patient's temperature was 98.8 on admission. On 22-JUL-2008, the patient experienced febrile neutropenia and was hospitalized. On 22-JUL-2008 an ECG showed atrial fibrillation, Q axis, left axis deviation, ST and T wave was abnormal, consider lateral ischemia or digitalis effect, moderate voltage criteria for LVH may be a normal variant. On 23-JUL-2008, a blood culture showed no growth in one day (negative). Urine cultures were also performed and were negative. The patient had one episode of fever that day and he was admitted but then remained afebrile afterwards. On 23-JUL-2008 the patient was treated with imipenem for febrile neutropenia, and vancomycin for skin MRSA. On 23-JUL-2008 a chest x-ray was performed. On 27-JUL-2008, the patient was in the hospital for neutropenic fever. The patient appeared to be improving and was scheduled for discharge when he began to complain of chest pain. He was diagnosed with myocardial infarction (grade 4) and was transferred to the coronary care unit. The myocardial infarction was treated with aspirin 81 mg daily, clopidogrel bisulfate (PLAVIX) 75mg, lisinopril daily, morphine sulfates, nitroglycerin, and labetalol was discontinued and carvedilol (COREG) 6.25mg was started. Cardiology felt that the patient was not a candidate for a stent, and medical management commenced plans to follow-up with his regular cardiologist after discharge. The patient's trans echo showed no evidence of vegetations, a mildly dilated left ventricle with severe global hypokineses and reduced systolic function; non dilated right ventricle with mildly reduced function. An AP chest x-ray showed internal development of diffuse left greater than the right parenchymal lung disease and bilateral

pleural effusions with cardiac enlargement compatible with congestive heart failure or pneumonia. On 27-JUL-2008 an ECG showed atrial fibrillation Q axis, left axis deviation. Minimal voltage criteria for LVH, may be normal variant, septal infarct, age undetermined. ON 27-JUL-2008 the patient was treated with senna for constipation and nitroglycerin for myocardial infarction. On 28-JUL-2008 the patient was treated with heparin for the myocardial infarction. On 28-JUL-2008 the patient experienced a troponin peak of 9. The patient had a non ST elevation MI. On 28-JUL-2008, a chest x-ray showed significant new areas of vascular congestion, cardiac silhouette enlarged, persistent small to moderate sized bilateral pleural effusions and increased areas of ground glass opacity centrally. The patient received a cardiac catheterization which revealed severe multi vessel disease and EF of 30 percent, left ventricular function depressed, recent NSTEMI infarct related artery not clearly defined at angiography, and significant systemic hypertension with mildly elevated left ventricular end diastolic pressure. On 28-JUL-2008 the patient was treated with midazolam hydrochloride (VERSED) as sedation for the procedure and labetalol during the cardiac catheterization. On 28-JUL-2008 the patient was treated with heparin for the myocardial infarction. On 29-JUL-2008, a chest x-ray showed persistent vascular congestion and small to moderate sized bilateral pleural effusions and no interval improvement which likely reflects pulmonary interstitial edema though pneumonia was not excluded. On 29-JUL-2008 the patient was treated with midazolam hydrochloride (VERSED) as sedation for the procedure and fentanyl as prophylaxis for pain during the procedure. On 30-JUL-2008, a chest x-ray revealed a persistent bilateral pleural effusions with improvement in a pulmonary edema pattern. On 30-JUL-2008 the patient was recovered from myocardial infarction (grade 4) and was discharged from the hospital with a discharge diagnoses of myocardial infarction, febrile neutropenia, and fever secondary to right groin cellulitis. The patient has an appointment for count checks and potential transfusions every other day post discharge. The patient was seen by an outside cardiologist upon discharge and continued with medical management. On 06-AUG-2008 the patient was seen by an oncologist and the decision was made to wait one week to decide whether to go forward with cycle 5 on study. On 13-AUG-2008 the patient was seen by the oncologist and evaluated. The decision was made by the physician and the patient to continue on the study. On 13-AUG-2008 the patient was started on cycle 5 study therapy and completed on 26-AUG-2008. On 24-SEP-2008 the patient was started on cycle 6 study therapy and completed on 07-OCT-2008.

The patient was also treated with the following medications: imipenem on 17-JUN-2008, benzocaine (+) butamben (+) tetracaine hydrochloride (CETACINE) on 29-JUL-2008 for a procedural premedication, aspirin on 27-JUL-2008 for coronary artery disease, lisinopril on 27-JUL-2008 for hypertension, aluminum hydroxide (+) magnesium hydroxide (MAALOX) on 27-JUL-2008 for GERD, eptifibatid on 28-JUL-2008 for coronary artery disease, furosemide (LASIX) in August 2008 for congestive heart failure, metronidazole (FLAGYL) on 09-AUG-2008 for clostridium defecile, and milk of magnesia on 16-AUG-2008 for constipation.

It was also reported that the patient experienced the following non-serious events: hyperglycemia and hyperbilirubinemia.

The reporting investigator felt that febrile neutropenia (grade 3) was related to study therapy with combination of vorinostat and decitabine. Myocardial infarction (grade 4) and groin cellulitis (grade 3) were not.

This is an amended report. The duration unit of days was added to the therapy for lisinopril.

Additional information is not expected.

6. Relevant tests/laboratory data, including dates

DIAGNOSTIC TEST

<u>Tests</u>	<u>Date</u>	<u>Value Unit</u>	<u>Normal Range</u>
computed axial tomography Comment: sinus	06/16/2008		
ultrasound Comment: kidney bilateral renal cysts with no hydronephrosis	06/23?/2008		
echocardiography	07/08/2008		
biopsy Comment: groin- abundant growth staphylococcus aureus methicillin resistant	07/09?/2008		
electrocardiogram Comment: atrial fibrillation, q axis, left axis deviation, ST and T wave abnormal	07/22/2008		
electrocardiogram Comment: consider lateral ischemia or digitalis effect, moderate voltage criteria for LVH may be nor	07/22/2008		
chest computed axial tomography Comment: without contrast see narrative	07/23?/2008		
chest X-ray Comment: see narrative	07/27/2008		
electrocardiogram Comment: atrial fibrillation q axis left axis deviation, minimal voltage criteria for LVH	07/27/2008		

electrocardiogram
Comment: may be normal variant, septal infarct, age undetermined
07/27/2008

chest X-ray
Comment: see narrative
07/28/2008

cardiac catheterization
Comment: see narrative
07/28/2008

chest X-ray
Comment: see narrative
07/29/2008

chest X-ray
Comment: see narrative
07/30/2008

LABORATORY RESULTS

Tests	Date	Value	Unit	Normal Range
WBC count	05/20/2008	1.4		
body temp	05/20/2008	100.1	F	
body temp	05/20/2008	100.4	F	
lymphocyte count	05/20/2008	76		
monocyte count	05/20/2008	0		
neutrophil count	05/20/2008	4		
wound culture Comment: negative	05/25/2008			
WBC count	05/28/2008	1.2		
lymphocyte count	05/28/2008	74		
monocyte count	05/28/2008	9		
neutrophil count	05/28/2008	12		
body temp	06/16/2008	101.3	F	
body temp	06/16/2008	100.8	F	
urine culture Comment: see narrative	06/16/2008			
body temp	07/21/2008	101.4	F	
body temp	07/21/2008	98.8	F	
blood culture Comment: no growth after one day	07/23/2008			
urine culture Comment: mixed microbial flora, consider urethral contamination	07/24/2008			

7. Other relevant history including preexisting medical conditions

Groin infection; Type 2 diabetes mellitus; Groin abscess; Anxiety; Hypokalaemia; Insomnia; Atrial fibrillation; Cholelithiasis; Dyspnoea exertional; Oedema lower limb; Fatigue; Hearing loss; Clostridium difficile infection; Constipation; Diabetes; Premedication; Rash; Urinary tract infection; Gastroesophageal reflux disease; Vomiting; Cardiac failure congestive; Nausea; Nausea prophylaxis; Infection prophylaxis; Acute myelocytic leukaemia; Arthroscopy L knee; Left ventricular dilatation; Q axis, left axis deviation; Dilatation atrial; Electrocardiogram T wave abnormal; Polymyalgia rheumatica; Pleural effusion; Urinary retention; Spinal operation; Shoulder pain; Hypokinesia

C. Suspect medication(s)

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

- #1 CAP vorinostat Unk
- #1 CAP vorinostat Unk
- #1 CAP vorinostat Unk
- #2 decitabine Unk
- #2 decitabine Unk
- #2 decitabine Unk
- #2 decitabine Unk
- #2 decitabine Unk

2. Dose, frequency & route used

- #1 400 mg/DAILY/PO
- #1 400 mg/DAILY/PO
- #1 400 mg/DAILY/PO
- #2 45 mg/Unk/IV
- #2 45.4 mg/Unk/IV
- #2 44.8 mg/Unk/IV
- #2 44.8 mg/Unk/IV
- #2 44.8 mg/Unk/IV

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

#1 04/30/2008 - 05/13/2008
 #1 05/28/2008 - 06/10/2008
 #1 07/02/2008 - 07/15/2008
 #2 03/31/2008 - 04/04/2008
 #2 04/30/2008 - 05/04/2008
 #2 05/28/2008 - 06/01/2008
 #2 07/02/2008 - 07/03/2008
 #2 07/05/2008 - 07/07/2008

4. Diagnosis for use (indication)

#1 Acute myelocytic leukaemia
 #1 Acute myelocytic leukaemia
 #1 Acute myelocytic leukaemia
 #2 Acute myelocytic leukaemia
 #2 Acute myelocytic leukaemia
 #2 Acute myelocytic leukaemia
 #2 Acute myelocytic leukaemia
 #2 Acute myelocytic leukaemia

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
#2				X

6. Lot # (if known)

#1
 #1
 #1
 #2
 #2
 #2
 #2
 #2

7. Exp date (if known)

#1
 #1
 #1
 #2
 #2
 #2
 #2
 #2

8. Event reappeared after reintroduction

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

C. Suspect medication(s)

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

BACTRIM DS TABLETS	07/11/2008 - 07/22/2008
COLACE	Unk - Cont
COMPazine	05/??/2008 - 07/21/2008
COREG	07/30/2008 - Cont
CRESTOR	07/27/2008 - 07/29/2008
CRESTOR	07/30/2008 - 07/30/2008
DIFLUCAN	06/27/2008 - 07/10/2008
FLOMAX (MORNIFLUMATE)	03/25/2008 - Cont
HIBICLENS	05/??/2008 - 07/22/2008
MUCOMYST	07/28/2008 - 07/30/2008
NORVASC	Unk - Cont
PLAVIX	07/27/2008 - Cont
PROTONIX	Unk - Cont
ROLAIDS	06/04/2008 - Cont
TUMS	06/04/2008 - Cont
ZOFRAN	03/31/2008 - Cont
ZOFRAN	05/??/2008 - 07/21/2008
ZOSYN	06/17/2008 - 06/17/2008
[therapy unspecified]	Unk - Cont
acetaminophen	03/26/2008 - Cont
acyclovir	04/02/2008 - Cont
allopurinol	03/25/2008 - 04/01/2008
allopurinol	04/03/2008 - Cont
chlorhexidine gluconate	03/27/2008 - 08/19/2008
digoxin	Unk - Cont
diphenhydramine hydrochloride	03/26/2008 - Cont
eptifibatide	07/28/2008 - 07/28/2008
labetalol hydrochloride	07/28/2008 - 07/28/2008
lisinopril	04/05/2008 - 05/15/2008
lisinopril	07/27/2008 - 07/29/2008
lorazepam	05/??/2008 - Cont
metformin	04/05/2008 - 07/22/2008
moxifloxacin hydrochloride	03/30/2008 - Cont
mupirocin	05/??/2008 - 07/30/2008
nystatin	03/26/2008 - Cont
oxycodone	Unk - Cont
vancomycin	06/17/2008 - 06/17/2008