

MERCK RESEARCH LABORATORIES

**Division of Merck & Co., Inc.
West Point, Pennsylvania 19486**

Date: November 13, 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 # 0801USA00427, GENSTUDY # 055-0013, AN # 1787

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 0801USA00427
UF/Dist report #	
FDA Use On	

A. Patient information

1. Patient identifier Unk AN 1787 in confidence	2. Age at time of event: or 64 years Date of Birth 07/27/1943	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 264 pounds
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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 checked="" type="checkbox"/> Death 06/06/2008 (mm/dd/yyyy)	<input checked="" 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) 12/30/2007	4. Date of this report (mm/dd/yyyy) 11/13/2008

5. Describe event or problem
This is in follow-up to report(s) previously submitted on 2/28/2008; 3/3/2008; 3/7/2008; 3/11/2008; 6/17/2008; 10/13/2008; 10/17/2008; 11/6/2008

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

Initial and follow up information has been received from an investigator concerning a 64 year old white male with congestive cardiac failure, fever, acid reflux, pleural effusions, thrombocytopenia (grade 3), degenerative joint disease, fatigue, hypertension, myeloproliferative disorder, osteoarthritis, anxiety, obesity, anaemia (grade 2), elevated blood count, hypokalemia, hyperuricemia, dry skin, general body pain, chronic peripheral edema, palpable splenomegaly, gingival bleeding, epistaxis, dizziness and a history of a past myocardial infarction in the midaxillary line of the 5th intercoastal space which was dime-sized, prior chemotherapy (hydroxurea October 2006) breath shortness,

(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: Breath shortness; Crackles; Diarrhoea; Breathing slowed; Headache; Chemotherapy; Myocardial infarction; Bleeding; Buccal mucosa ulceration; Jugular vein distension CONCURRENT CONDITIONS: Cardiac failure congestive; Hyperuricaemia; Hypokalaemia; White blood cell count abnormal; Oesophageal

(Continued on Additional Page)

C. Suspect medication(s)

1. Name (Give labeled strength & mfr/labeler)	
# 1 CAP vorinostat Unk	
# 2 INJ decitabine Unk	
2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
# 1 400 mg/DAILY/PO	# 1 12/18/2007 - 12/30/2007
# 2 48 mg/DAILY/IV	# 2 12/18/2007 - 12/22/2007
4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced.
# 1 Acute myelocytic leukaemia	yes no N/A unk
# 2 Acute myelocytic leukaemia	# 1 <input checked="" 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 checked="" type="checkbox"/>
10. Concomitant medical products and therapy dates (excluded treatment of event)	
DIFLUCAN	12/13/2007-01/01/2008
EUCERIN CREME	01/??/2008-Cont

(Continued on Additional Page)

G. All manufacturers

1. Contact office - name/address Merck Human Health Division Merck & Co., Inc. P.O. Box 4 West Point, PA 19486-0004 ATTN: Worldwide Product Safety	2. Phone Number (215) 652-8071
4. Date received by manufacturer (mm/dd/yyyy) 10/29/2008	3. Report source (check all that apply)
6. If IND, protocol # 0550013	<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
7. Type of report <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# 8	5. (A)NDA # 21991 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 WAES 0801USA00427	

8. Adverse event term(s) HAEMATEMESIS; VOMITING; NAUSEA; ACUTE MYELOID LEUKAEMIA

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

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.

5. Describe event or problem

crackles, breathing slowed, diarrhoea, headache, jugular vein distension, bleeding and buccal mucosa ulceration who entered a study title as stated above. On 17-DEC-2007, the patient's absolute blood neutrophil count was reported as 22.6 and his blasts were reported as 58. On 18-DEC-2007, the patient was placed on cycle 1 study therapy with vorinostat, capsule, 400 mg daily for the treatment of acute myelocytic leukaemia (diagnosed in November 2007; disease progression 11-DEC-2007). Concomitant study therapy included decitabine IV 20 mg/m². Concomitant therapy included furosemide sodium (LASIX (furosemide sodium)), potassium chloride (K-DUR), betaxolol HCl, lansoprazole (PREVACID), vitamins (unspecified), deferasirox (EXJADE), loperamide HCl (IMODIUM), acetaminophen (TYLENOL), ciprofloxacin, fluconazole (DIFLUCAN), valacyclovir hydrochloride (VALTREX), allopurinol, levofloxacin (LEVAQUIN), potassium chloride, chloride, mineral oil (+) petrolatum (EUCERIN CREME), hydroxyurea (HYDREA). On this day, the patient's absolute blood neutrophil count was reported as 20.8 and his blasts were reported as 59. On 30-DEC-2007 the patient experienced nausea (grade 3), and hematemesis (grade 3). On 31-DEC-2007, the patient was admitted from the clinic with vomiting (grade 3), nausea (grade 3) and hematemesis (grade 3). Vital signs at admission were temperature 99, pulse 65 and Respirations 16. Laboratory diagnostic studies on admission were reported as white blood cell count (WBC) 6.7; hemoglobin blood test (HGB) 8.6 g/dL, platelets 9; blood urea nitrogen (BUN) 20 mg/dL; creatinine 1.3 mg/dL; K 3.5 mmol/L; serum sodium test (NA) 138 mmol/L; serum magnesium test (Mg) 2.2 mg/dL. Study therapy was interrupted. Vomiting was treated with ondansetron hydrochloride (ZOFTRAN), "PPI" and diet reduction to clear liquids. The diet was advanced as tolerated on 02-JAN-2008. Vital signs were reported as temperature 98.2, Pulse 78, Respirations 16, blood pressure (BP) 130/67. No hematemesis since admission was reported. On 31-DEC-2007, the patient was placed on therapy with ondansetron hydrochloride (ZOFTRAN) and prochlorperazine maleate (COMPAZINE) for nausea and vomiting and pantoprazole sodium (PROTONIX) for acid reflux. 01-JAN-2008 the patient was administered prochlorperazine maleate (COMPAZINE), 40 mg PRN IV infusion for the treatment of nausea. On 01-JAN-2008 at 02:20, the patient developed worsening hypokalemia (NSAE) and was treated with dibasic (+) potassium phosphate, monobasic (+) sodium phosphate, dibasic (+) sodium phosphate, monobasic (NEUTRA-PHOS) on 02-JAN-2008 as a one time dose. On 02-JAN-2008 the patient recovered from hypokalemia. On 01-JAN-2008, laboratory diagnostic studies included: WBC of 6.6, serum bicarbonate of 25, serum blood urea nitrogen of 14, serum calcium of 8.3, serum chloride of 106, serum creatinine of 1.2, serum phosphorus of 2.5, serum potassium of 3.3, serum sodium of 141. On 02-JAN-2008, the patient was recovered and discharged. Discharge labs were reported as WBC 9.2; Mg 2.1 mg/dL; BUN 10 mg/dL K 3.5 mmol/L; Mg 2.1 mg/dL; BUN 10 mg/dL; Creatinine 1.1 g/dL; HGB 8.8 g/dL; Na 142 mmol/L; and platelets 28. The discharge diagnoses was reported to be nausea and vomiting. As of 03-JAN-2008, the vomiting and nausea grade was reduced to grade 2. It was also reported that the patient continued to take ondansetron hydrochloride (ZOFTRAN) 3 times a day as well as compazine for nausea and vomiting. He was advised to eat small frequent meals. The antibiotics were discontinued. Hematemesis was concluded to be secondary to thrombocytopenia, no endoscopy was indicated at that time. On 08-JAN-2008, the patient was discontinued from the study for the reason of progressive disease. On 06-JUN-2008, the patient died from worsening acute myeloid leukemia.

The patient received the following treatment during study: acetaminophen (TYLENOL) given on 31-DEC-2007 650 mg one time dose for prophylaxis prior to blood products, diphenhydramine hydrochloride (BENADRYL) administered on 31-DEC-2007 one time dose of 25 mg for prophylaxis prior to blood products.

The reporting investigator felt that hematemesis (grade 3), vomiting (grade 3), and nausea (grade 3) were related to study therapy.

The reporting investigator felt that worsening of AML (grade 5) was not related to the study therapy.

Hematemesis (grade 3) was considered to be disabling.

This is an amended report. The worsening of AML (grade 5) was changed to not related to the study therapy in the narrative.

Additional information is not expected.

6. Relevant tests/laboratory data, including dates

DIAGNOSTIC TEST

Tests	Date	Value Unit	Normal Range
electrocardiogram Comment: premature ventricular contractions	12/18/2007		
electrocardiogram Comment: premature atrial contraction	12/21/2007		
blood pressure measurement	01/02/2008	130/67	

LABORATORY RESULTS

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(continued)

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
APTT				
INR	12/13/2007			
WBC count	12/13/2007	1.4		
hematocrit	12/13/2007	98.9		
hemoglobin	12/13/2007	19		
lymphocyte count	12/13/2007	6.9		
monocyte count	12/13/2007	18		
neutrophil count	12/13/2007			
platelet count	12/13/2007	14		
serum LDH	12/13/2007	34		
serum alanine aminotransferase	12/13/2007	606		
serum albumin	12/13/2007	19		
serum alkaline phosphatase	12/13/2007	3.8		
serum aspartate aminotransferase	12/13/2007	77		
serum bicarbonate	12/13/2007	33		
serum blood urea nitrogen	12/13/2007	28		
serum calcium	12/13/2007	23		
serum chloride	12/13/2007	8.9		
serum creatinine	12/13/2007	103		
serum direct bilirubin	12/13/2007	1.1		
serum gamma glutamyl transferase	12/13/2007			
serum glucose	12/13/2007	149		
serum phosphorus	12/13/2007	114		
serum potassium	12/13/2007	3		
serum sodium	12/13/2007	3.9		
serum uric acid	12/13/2007	139		
total serum bilirubin	12/13/2007	10.2		
total serum protein	12/13/2007	0.8		
mean corpuscular volume	12/13/2007	6.6		
prothrombin time	12/13/2007	85		
red blood cell count	12/13/2007	14		
absolute neutrophil count	12/13/2007	2.3		
urinalysis	12/17/2007	22.6		
blast cell observation	12/17/2007			
APTT	12/17/2007	58		
INR	12/18/2007	31.3		
WBC count	12/18/2007	1.3		
absolute neutrophil count	12/18/2007	74.3		
hematocrit	12/18/2007	20.8		
hemoglobin	12/18/2007	29		
lymphocyte count	12/18/2007	10.6		
monocyte count	12/18/2007	8		
neutrophil count	12/18/2007	2		
platelet count	12/18/2007	28		
serum LDH	12/18/2007	26		
serum alanine aminotransferase	12/18/2007	565		
serum albumin	12/18/2007	25		
serum alkaline phosphatase	12/18/2007	3.9		
serum aspartate aminotransferase	12/18/2007	84		
serum bicarbonate	12/18/2007	36		
serum blood urea nitrogen	12/18/2007	32		
serum calcium	12/18/2007	20		
serum chloride	12/18/2007	9.3		
serum creatinine	12/18/2007	103		
serum direct bilirubin	12/18/2007	1		
serum gamma glutamyl transferase	12/18/2007	0.2		
serum glucose	12/18/2007	184		
serum phosphorus	12/18/2007	97		
serum potassium	12/18/2007	3.9		
serum sodium	12/18/2007	3.5		
serum uric acid	12/18/2007	141		
total serum bilirubin	12/18/2007	9.8		
total serum protein	12/18/2007	0.8		
mean corpuscular volume	12/18/2007	6.8		
prothrombin time	12/18/2007	86		
red blood cell count	12/18/2007	13.2		
blast cell observation	12/18/2007	3.4		
APTT	12/18/2007	59		
INR	12/26/2007			
WBC count	12/26/2007			
hematocrit	12/26/2007	8.7		
hemoglobin	12/26/2007	28		
lymphocyte count	12/26/2007	9.2		
monocyte count	12/26/2007	20		
neutrophil count	12/26/2007	1		
platelet count	12/26/2007	48		
	12/26/2007	11		

serum LDH	12/26/2007	463
serum LDH	12/26/2007	463
serum alanine aminotransferase	12/26/2007	13
serum albumin	12/26/2007	3.7
serum alkaline phosphatase	12/26/2007	82
serum aspartate aminotransferase	12/26/2007	21
serum bicarbonate	12/26/2007	28
serum blood urea nitrogen	12/26/2007	31
serum calcium	12/26/2007	8.7
serum chloride	12/26/2007	102
serum creatinine	12/26/2007	1.3
serum direct bilirubin	12/26/2007	
serum gamma glutamyl transferase	12/26/2007	134
serum glucose	12/26/2007	134
serum phosphorus	12/26/2007	4.3
serum potassium	12/26/2007	3.9
serum sodium	12/26/2007	136
serum uric acid	12/26/2007	7.3
total serum bilirubin	12/26/2007	1
total serum protein	12/26/2007	6.3
mean corpuscular volume	12/26/2007	86
red blood cell count	12/26/2007	3.2
prothrombin time	12/26/2007	
WBC count	12/31/2007	6.7
hemoglobin	12/31/2007	8.6 g/dL
plasma blood urea nitrogen	12/31/2007	20 mg/dL
platelet count	12/31/2007	9
serum creatinine	12/31/2007	1.3 mg/dL
serum magnesium	12/31/2007	2.2 mg/dL
serum potassium	12/31/2007	3.5 mmol/L
serum sodium	12/31/2007	138 mmol/L
vital sign	12/31/2007	

Comment: T = 99, P= 65, R=16

APTT	01/01/2008	
INR	01/01/2008	
WBC count	01/01/2008	6.6
hematocrit	01/01/2008	26
hemoglobin	01/01/2008	8.6
lymphocyte count	01/01/2008	11
monocyte count	01/01/2008	
neutrophil count	01/01/2008	13
platelet count	01/01/2008	33
serum LDH	01/01/2008	235
serum alanine aminotransferase	01/01/2008	11
serum albumin	01/01/2008	3.7
serum alkaline phosphatase	01/01/2008	66
serum aspartate aminotransferase	01/01/2008	16
serum bicarbonate	01/01/2008	25
serum blood urea nitrogen	01/01/2008	14
serum calcium	01/01/2008	8.3
serum chloride	01/01/2008	106
serum creatinine	01/01/2008	1.2
serum direct bilirubin	01/01/2008	
serum gamma glutamyl transferase	01/01/2008	86
serum glucose	01/01/2008	113
serum phosphorus	01/01/2008	2.5
serum potassium	01/01/2008	3.3
serum sodium	01/01/2008	141
serum uric acid	01/01/2008	4.8
total serum bilirubin	01/01/2008	0.9
total serum protein	01/01/2008	6.3
mean corpuscular volume	01/01/2008	87
prothrombin time	01/01/2008	
red blood cell count	01/01/2008	3
WBC count	01/02/2008	9.2
hemoglobin	01/02/2008	8.8 g/dL
serum blood urea nitrogen	01/02/2008	10 mg/dL
serum creatinine	01/02/2008	1.1
serum magnesium	01/02/2008	2.1 mg/dL
serum potassium	01/02/2008	3.5 mmol/L
serum sodium	01/02/2008	142 mmol/L
vital sign	01/02/2008	

Comment: T=98.2, P=78, R=16

APTT	01/07/2008	
INR	01/07/2008	
WBC count	01/07/2008	45.9
hematocrit	01/07/2008	26

hemoglobin	01/07/2008	8.7
lymphocyte count	01/07/2008	13
monocyte count	01/07/2008	1
neutrophil count	01/07/2008	3
platelet count	01/07/2008	95
serum LDH	01/07/2008	475
serum alanine aminotransferase	01/07/2008	15
serum albumin	01/07/2008	3.8
serum alkaline phosphatase	01/07/2008	75
serum aspartate aminotransferase	01/07/2008	29
serum aspartate aminotransferase	01/07/2008	29
serum bicarbonate	01/07/2008	30
serum blood urea nitrogen	01/07/2008	18
serum calcium	01/07/2008	9.3
serum chloride	01/07/2008	99
serum creatinine	01/07/2008	1.1
serum direct bilirubin	01/07/2008	
serum gamma glutamyl transferase	01/07/2008	115
serum glucose	01/07/2008	99
serum phosphorus	01/07/2008	4.1
serum potassium	01/07/2008	3.9
serum sodium	01/07/2008	136
serum uric acid	01/07/2008	6.3
total serum bilirubin	01/07/2008	0.7
total serum protein	01/07/2008	6.8
mean corpuscular volume	01/07/2008	87
prothrombin time	01/07/2008	
red blood cell count	01/07/2008	3

7. Other relevant history including preexisting medical conditions

acid reflux; Thrombocytopenia; Pleural effusion; Dry skin; General body pain; Obesity; Iron increased; Vomiting; Fever; Dizziness; Hyperuricaemia; Epistaxis; Splenomegaly; Gingival bleeding; Chronic oedema of legs; Vitamin supplementation; Antifungal prophylaxis; Fatigue; Hypertension; Myeloproliferative disorder; Anxiety; Osteoarthritis; Degenerative joint disease; Anaemia

C. Suspect medication(s)

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

EXJADE	01/01/2007 - 12/31/2007
HYDREA	11/??/2007 - 12/23/2007
HYDREA	01/08/2008 - Cont
IMODIUM	01/01/2007 - Cont
K-DUR	01/??/2007 - Cont
LASIX (FUROSEMIDE SODIUM)	01/01/2007 - Cont
LEVAQUIN	12/20/2007 - Cont
PREVACID	04/??/2007 - Cont
TYLENOL	01/01/2007 - Cont
VALTREX	12/13/2007 - 01/02/2008
allopurinol	12/20/2007 - Cont
betaxolol hydrochloride	01/??/2007 - Cont
ciprofloxacin	12/14/2007 - 01/02/2008
potassium chloride	01/??/2007 - Cont
vitamins (unspecified)	01/01/2007 - Cont
vitamins (unspecified)	Unk - Unk