

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

December 31, 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 # 0802USA01530, GENSTUDY # 0550007, AN # 1790

# 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

Page 1

Mfr report #	WAES 0802USA01530
UF/Dist report #	
	FDA Use On

A. Patient information			
1. Patient identifier Unk  AN 1790  in confidence	2. Age at time of event: or 75 years  Date of Birth: 08/06/1932	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight  158 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) 01/31/2008		4. Date of this report (mm/dd/yyyy) 12/31/2008	
5. Describe event or problem			
This is in follow-up to report(s) previously submitted on 10/1/2008; 10/3/2008; 10/16/2008			
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 75 year old white male with hypertension, irritable bowel syndrome, cramp, benign prostatic hyperplasia, gastroesophageal reflux disease, benign prostatic hypertrophy, eczema, atrioventricular block first degree, prophylaxis for viral infection, nausea and irritable bowel syndrome, hyponatraemia and a history of basal cell carcinoma excision, diarrhoea, pneumonia fungal, klebsiella bacteraemia, diabetes mellitus non-insulin-dependent, acute renal insufficiency, ventral hernia repair and thoracentesis and prior chemotherapy with cytarabine and daunorubicin (10-JUN-2004), high dose cytarabine hiDAC (03-AUG-2004) and tipifarnib (ZARNESTRA) (03-JUN-2005) who entered 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: Basal cell carcinoma excision; Diarrhoea; Pneumonia fungal; Acute renal insufficiency; Diabetes mellitus non-insulin-dependent; Chemotherapy; Klebsiella bacteraemia; Ventral hernia repair; Thoracentesis CONCURRENT CONDITIONS: Hypertension; Sinus congestion; Deep vein thrombosis; Deep			
(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 01/15/2008 - 01/28/2008	
# 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"/>	
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)			
COLACE		01/20/2008-01/21/2008	
COUNADIN		08/12/2008-08/15/2008	
(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
4. Date received by manufacturer (mm/dd/yyyy) 12/19/2008	3. Report source. (check all that apply)
6. If IND, protocol # 0550007	<input type="checkbox"/> foreign
7. Type of report	<input checked="" type="checkbox"/> study
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day	<input type="checkbox"/> literature
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic	<input type="checkbox"/> consumer
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial	<input checked="" type="checkbox"/> health professional
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 3	<input type="checkbox"/> user facility
5. (A)NDA # 21991 IND # 58915 STN # PMA/ 510(k) #	<input type="checkbox"/> company representative
Combination Product <input type="checkbox"/> Yes	<input type="checkbox"/> distributor
Pre-1938 <input type="checkbox"/> Yes	<input type="checkbox"/> other:
OTC product <input type="checkbox"/> Yes	
9. Mfr. report number	
WAES 0802USA01530	

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

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

study, title as stated above. On 14-JAN-2008, laboratory diagnostic studies included an electrocardiogram (ECG) with results reported as atrioventricular block first degree. On 15-JAN-2008, the patient was placed on therapy with vorinostat, capsule, 400 mg, once a day for the treatment of acute myelocytic leukaemia (diagnosed 10-JAN-2004 with most recent diagnosis on 06-JAN-2008). Concomitant study therapy included decitabine 20 mg/m<sup>2</sup> (37.4 mg) administered IV daily on days 1-5. Other concomitant therapy included valsartan (DIOVAN), dicyclomine HCl, vitamins (unspecified), acyclovir, ondansetron, magnesium (unspecified), tamsulosin hydrochloride (FLOMAX), fish oil, calcium carbonate (TUMS), loperamide hydrochloride (IMODIUM), pantoprazole, allopurinol and docusate sodium (COLACE).

On 16-JAN-2008, laboratory diagnostic studies included an ECG with results reported as atrioventricular block first degree. On 28-JAN-2008 laboratory diagnostic studies included lymphocyte count 74, monocyte count 2.9, neutrophil count 22.1 and white blood cell count of 1. On 31-JAN-2008, the patient presented to the clinic with erythema of the upper lip but was afebrile. He was given antibiotics to take home. "He went to the infusion for blood products." The patient was given acetaminophen (TYLENOL) 325 mg as needed and diphenhydramine hydrochloride (BENADRYL) 25 mg as needed as premedication for the blood products. RBC's were hung at 13:30. At 14:20 the patient became febrile with a temperature of 100.9 (neutropenic fever (grade 3)). Etiology was unknown. Cellulitis was not the underlying cause of the fevers. Fever could likely have been transfusion reaction or just a result of low counts and disease. The infection coinciding with upper lip erythematous rash (cellulitis) (NSAE) was suspected. Blood and urine cultures were drawn. The patient was treated with moxifloxacin hydrochloride (AVELOX), 400 mg and cephalexin (KEFLEX), 500 mg for lip infection. At 17:30, the patient was admitted to the hospital in an inpatient unit. A computed axial tomography (CT scan) of the chest and face was reported as no new chest modules, left perimandibular soft tissue swelling, no fluid or lymphadenopathy. Blood and urine cultures remained negative throughout admission. The patient remained neutropenic with WBC of 0.7 and neutrophils of 12%, but without a fever. The course of treatment was intravenous antibiotic administration (Cefepime and Vancomycin), chest and facial bone CT scan and repeat blood cultures with subsequent fever spikes. The patient remained afebrile and blood cultures remained negative throughout admission.

On 04-FEB-2008, laboratory diagnostic studies performed included lymphocyte count 77, monocyte count 11, neutrophil count 8 and white blood cell count of 0.8. The patient remained a febrile, blood and urine cultures remained negative for bacteria throughout admission and since the patient had no fever on 06-FEB-2008 the patient was discharged on cephalexin (KEFLEX) and clindamycin 450 mg four times a day. The patient was scheduled for follow up in the clinic on 11-FEB-2008. He had been asked to call the clinic or go to the nearest emergency room if he developed a fever. His discharge diagnosis was neutropenic fever, cellulitis. In February (date unspecified) the patient was treated with compazine 10 mg as needed for nausea and "ergocalciferol" 200 international units as vitamin D supplement. On 12-FEB-2008, the patient began cycle 2 of therapy with vorinostat, 400 mg daily for 14 days and decitabine 20 mg/m<sup>2</sup> for 5 days. On 13-FEB-2008, an ECG was performed which again resulted as atrioventricular block first degree. On 11-MAR-2008, the patient began cycle 3 of therapy with vorinostat, 400 mg daily for 14 days and decitabine 20mg/m<sup>2</sup> for 5 days.

On 21-APR-2008, 02-JUN-2008 and 14-JUL-2008, the patient began cycles 4, 5 and 6, of therapy with vorinostat, 400 mg daily for 14 days and decitabine 20 mg/m<sup>2</sup> for 5 days, respectively. Laboratory diagnostic studies included lymphocyte count 90, monocyte count 7, neutrophil count 3 and white blood cell count of 1 and an absolute blood neutrophil count of 30.

On 11-AUG-2008, the patient was seen in the clinic and was asymptomatic. Overnight he spiked a fever, called and was instructed to return for admission. On 12-AUG-2008, the patient developed neutropenic fever (grade 3) and was hospitalized. Cultures were taken which showed Coag negative Staph and the patient was treated with vancomycin 1 gm every 12 hours for three days during admission and imipenem (+) cilastatin sodium, infusion (form), 500 mg, 1X on 12-AUG-2008. From 13-AUG-2008 thru 18-AUG-2008, the patient was treated with cefepime infusion (form), 2 grams, three times a day, IV. No further positive cultures were reported during admission. On 15-AUG-2008, the patient recovered from the neutropenic fever (grade 3). On 18-AUG-2008, the patient was discharged from the hospital on moxifloxacin hydrochloride (AVELOX) 400 mg daily PO. Discharge diagnoses were reported as bacteremia and deep vein thrombosis at PICC site. No further positive cultures were reported during outpatient follow-up and the patient remained afebrile. The patient continued in the study without interruption. On 25-AUG-2008 and 06-OCT-2008, the patient began cycle 7 and 8 of therapy with decitabine 20 mg/m<sup>2</sup> for 5 days and vorinostat 400 mg daily for 14 days.

Other treatment medications used during the study included: prochlorperazine maleate (COMPAZINE) (February 2008) 10 mg as needed for nausea, ergocalciferol, (February 2008), 200 IU daily for vitamin D supplement, acetaminophen (+) propoxyphene napsylate (DARVOCECT), 100 mg, 11-JUN-2008 thru 02-OCT-2008, PRN for pain, magnesium sulfate, 3 grams, 1X, IV on 13-AUG-2008 as nutritional supplement, voriconazole, tablet, 200 mg, BID 13-AUG-2008 thru 13-AUG-2008 for fungal prophylaxis, warfarin sodium (COUMADIN), tablet, 5 mg, daily 12-AUG-2008 thru 15-AUG-2008 for DVT prophylaxis, heparin, infusion (form), 12-AUG-2008 thru 13-AUG-2008 for DVT and cough, cold, and flu therapies,







C. Suspect medication(s)

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

DARVOCET-N	06/11/2008 - 10/02/2008
DIOVAN	01/??/2007 - Cont
FLOMAX (TAMSULOSIN HYDROCHLORIDE)	Unk - Cont
IMODIUM	Unk - Cont
PROTONIX	01/16/2008 - 01/24/2008
PROTONIX	08/12/2008 - 08/18/2008
TUMS	Unk - Cont
acyclovir	01/15/2008 - Cont
allopurinol	01/16/2008 - 01/21/2008
cough, cold, and flu therapies	(07/??/2008 - Cont
dicyclomine hydrochloride	Unk - Cont
heparin	08/12/2008 - 08/13/2008
magnesium (unspecified)	Unk - Cont
magnesium sulfate	08/13/2008 - 08/13/2008
omega-3 marine triglycerides	Unk - Cont
ondansetron	01/15/2008 - Cont
vitamins (unspecified)	Unk - Cont
voriconazole	08/12/2008 - 08/13/2008