

# MERCK RESEARCH LABORATORIES

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

Date: November 12, 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 # 0510CHE00016, GENSTUDY # 016-0002, AN # 606

The FDA Medical Products Reporting Program

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Mfr report #	WAES 0510CHE00016
UF/Dist report #	
FDA Use Only	

### A. Patient information

1. Patient identifier Unk AN 606 in confidence	2. Age at time of event or 69 years Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 121 lbs
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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 01/12/2006 (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) 10/18/2005	4. Date of this report (mm/dd/yyyy) 11/12/2008

5. Describe event or problem  
This is in follow-up to report(s) previously submitted on 10/25/2005; 11/8/2005; 2/6/2006; 2/9/2006; 2/16/2006; 10/7/2008; 10/29/2008; 11/7/2008

Phase I Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (L-001079038) in Combination With Bexarotene in Patients With Advanced Cutaneous T-Cell Lymphoma

Information has been received from an investigator concerning a 69 year old female with diabetes mellitus, hypochromic anaemia, dyspnoea, pericardial effusion, hypothyroidism, nocturia, cutaneous t-cell lymphoma, hypercholesterolaemia and insomnia and a history of icterus, hysterectomy, vasculitis, colitis haemorrhagic, cystitis, herpes zoster, herpes simplex, hyperlipidaemia, gallbladder stone, radiotherapy and surgery (oncologic) who entered a study, title as stated above. On 21-SEP-2005 the patient was placed on vorinostat, tablet, 200 mg, once a day for the treatment of cutaneous t-cell lymphoma. Concomitant therapy included bexarotene (TARGRETIN), tablet, 225 mg, once a day for the treatment

(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.)  
MEDICAL HISTORY: Icterus; Hysterectomy; Vasculitis; Colitis haemorrhagic; Cystitis; Herpes simplex; Gallbladder stone; Hyperlipidaemia; Radiotherapy; Surgery; Herpes zoster  
CONCURRENT CONDITIONS: Diabetes mellitus; Pericardial effusion; Hypercholesterolaemia; Cancer pain; Cutaneous T-cell lymphoma;

(Continued on Additional Page)

### C. Suspect medication(s)

1. Name (Give labeled strength & mfr/labeler)	
# 1 CAP vorinostat Unk	
# 2 TAB bexarotene Unk	
(Continued on Additional Page)	
2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
# 1 200 mg/DAILY/PO	# 1 09/21/2005 - 11/02/2005
# 2 225 mg/DAILY/PO	# 2 09/21/2005 - 11/02/2005
4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced.
# 1 Cutaneous T-cell lymphoma	yes no N/A unk
# 2 Cutaneous T-cell lymphoma	# 1 <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>
6. Lot #	7. Exp. Date
# 1	# 1
# 2	# 2
8. Event reappeared after reintroduction.	
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"/>	
9. NDC # or Unique ID	
Unknown	
10. Concomitant medical products and therapy dates (excluded treatment of event)	
[therapy unspecified]	09/13/2005 - Cont
acetaminophen	09/13/2005 - 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: Worldwide Product Safety	(215) 652-8071
4. Date received by manufacturer (mm/dd/yyyy) 10/28/2008	3. Report source. (check all that apply)
6. If IND, protocol # 0160002	<input checked="" 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# 8	<input type="checkbox"/> user facility
5. (A)NDA # 21991	<input type="checkbox"/> company representative
IND # 58915	<input type="checkbox"/> distributor
STN #	<input type="checkbox"/> other:
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 .0510CHE00016

8. Adverse event term(s) T-CELL LYMPHOMA; SOMNOLENCE; CANCER PAIN; HEPATIC FAILURE; NEOPLASM PROGRESSION
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### 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

## B. Adverse event or product problem

## 5. Describe event or problem

of cutaneous t-cell lymphoma. Other concomitant therapy included glimepiride (AMARYL), ibuprofen (BRUFEN), acetaminophen (DAFALGAN), cetirizine hydrochloride (ZYRTEC), povidone-iodine (BETADINE), simvastatin (MSD), oxazepam (SERESTA), tramadol HCl (TRAMAL) and [therapy unspecified] (JALUGEN). On 18-OCT-2005 the patient experienced worsening of cutaneous t cell lymphoma (grade 3) and worsening of CTLC lesion pain (grade 3, event of clinical interest, non-serious) and was hospitalized. Therapy with vorinostat continued. At the time of this report the patient's worsening of cutaneous t cell lymphoma persisted. The reporter felt that worsening of cutaneous t cell lymphoma is possibly related to therapy with vorinostat (because of not yet responding to therapy with vorinostat and progression and exulzeration of the tumors the patient had to be hospitalized).

Follow up information was received on 26-OCT-2005. Worsening of cutaneous t cell lymphoma was upgraded to other important medical event by the investigator. The reporter felt that worsening of cutaneous t cell lymphoma is probably not related to therapy with vorinostat. The patient is still hospitalized and another treatment (chemotherapy) has to be started.

Follow up information was received on 03-NOV-2005. Serious criteria was described as cancer and hospitalization, not as other important medical event by the investigator.

On 11-NOV-2005 new information was received. On 11-NOV-2005 the patient experienced somnolence. The morphine medication was increased during hospitalization from 18-OCT-2005 till 08-NOV-2005, at home the patient was free to take more morphine drops if necessary up to 10 drops per hour. Because of the pain the patient took morphine medication and couldn't be waken up by her daughter in the morning of 11-NOV-2005 and was hospitalized. Therapy with morphine was reduced and the patient recovered from somnolence. On 18-NOV-2005 the patient was transferred to another hospital for the treatment of the cutaneous t cell lymphoma. The reporter felt that somnolence was definitely not related to therapy with vorinostat, but probably related to therapy with morphine. Therapy with vorinostat was discontinued on 02-NOV-2005 due to study stop.

On 23-JAN-2006 hospitalization report was received from the investigator. On 18-NOV-2005 the patient was transferred to another hospital for the treatment of the cutaneous t cell lymphoma. On 10-JAN-2006 the patient was transferred back to the previous hospital. General condition of the patient was reduced, cutaneous t cell lymphoma was advanced, onset of hepatic insufficiency was diagnosed. On approximately 16-JAN-2006 the patient died. At the time of this report no death report was available. Further information has been requested and will be provided upon receipt of the patient's death report.

On 31-JAN-2006 follow up information was received. From the data which is available at the moment the patient died from organ failure (mainly liver) and progression of disease incl. bacterial superinfection of the CTCL tumors. Therefore death is currently rated as not-drug related. Further information has been requested and will be provided upon receipt of the patient's death report.

On 01-FEB-2006 the investigator confirmed that the highest probability for the patient's death is tumor progression with drug causality of not related.

On 10-FEB-2006 discharge letter from the hospital where the patient died was received. Exitus letalis on 12-JAN-2006. According to this letter the investigator confirmed that the highest probability for the patient's death is tumor progression with drug causality of not related.

On 02-OCT-2008 additional information was received via study correction that the patient had T-cell lymphoma, diagnosed in 2005, as concurrent condition.

On 23-OCT-2008 additional information was received via study correction that T-cell lymphoma was not considered to be cancer.

On 28-OCT-2008 additional information was received via study correction that concurrent condition "T-cell lymphoma" was changed to "cancer pain" and that concurrent condition "cutaneous T-cell lymphoma" was introduced. Morphine was used as concomitant therapy. The adverse event term "death" was changed to "tumor progression".

No further information is available.

## Lab values:

18-Oct-2005

serum C-reactive protein: 112mg/l (abnormal range)

serum calcitonin: 0.4 ng/l (normal range)

## 6. Relevant tests/laboratory data, including dates

## LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u> <u>Unit</u>	<u>Normal Range</u>
serum C-reactive protein Comment: abnormal range	10/18/2005	112 mg/l	- 5
serum calcitonin test Comment: normal range	10/18/2005	0.4 ng/l	- 0.5

## 7. Other relevant history including preexisting medical conditions

Insomnia; Hypothyroidism; Nocturia; Hypochromic anaemia; Dyspnoea

## C. Suspect medication(s)

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

#3 morphineso4 Unk

## 2. Dose, frequency &amp; route used

#3 Unk/Unk/PO

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

#3 Unk - Cont

## 4. Diagnosis for use (indication)

#3 Cutaneous T-cell lymphoma

## 5. Event abated after use stopped or dose reduced

YES	NO	N/A	UNK
			X

## 6. Lot # (if known)

#3

## 7. Exp date (if known)

#3

## 8. Event reappeared after reintroduction

YES	NO	N/A	UNK
			X

## C. Suspect medication(s)

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

cetirizine hydrochloride	09/13/2005 - Cont
glimepiride	08/??/2004 - Cont
ibuprofen	08/09/2005 - Cont
oxazepam	09/21/2005 - Cont
povidone-iodine	?/?/2001 - Cont
simvastatin	09/16/2005 - Cont
tramadol hydrochloride	09/13/2005 - 09/26/2005
tramadol hydrochloride	09/27/2005 - 10/06/2005
tramadol hydrochloride	10/07/2005 - Cont