

MERCK RESEARCH LABORATORIES

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

13-NOV-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 # 0512DEU00091, GENSTUDY # 016-003, AN#: 612

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 0512DEU00091
UF/Dist report #	
FDA Use Only	

A. Patient information			
1. Patient identifier Confidential AN 612 in confidence	2. Age at time of event or Date of Birth: 40 years	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight Unk

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)	4. Date of this report (mm/dd/yyyy)
12/15/2005	11/13/2008

5. Describe event or problem
This is in follow-up to report(s) previously submitted on 12/22/2005; 12/28/2005; 12/30/2005; 1/13/2006

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 40 year old male with arthrosis, allergic rhinoconjunctivitis, hypothyroidism and a history of appendicectomy who entered a study, title as stated above.

On 28-SEP-2005, the patient was placed on therapy with vorinostat, capsule, 200 mg, once a day for the treatment of cutaneous T-cell lymphoma and with bexarotene, capsule, 150 mg/m2 once a day for the treatment of cutaneous T-cell lymphoma. Concomitant therapy included fenofibrate and levothyroxine sodium.

Subsequently, the patient developed the following

(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: Appendicectomy CONCURRENT CONDITIONS: Arthrosis; Allergic rhinoconjunctivitis; Hypothyroidism

C. Suspect medication(s)	
1. Name (Give labeled strength & mfr/labeler)	
# 1 CAP vorinostat 100 mg	
# 2	
(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 09/28/2005 - 12/21/2005
# 2	# 2
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	# 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	6. 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 type="checkbox"/>
10. Concomitant medical products and therapy dates (excluded treatment of event)	
fenofibrate	09/08/2005 - Cont
levothyroxine sodium	10/12/2005 - Cont

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	(215) 652-8071
ATTN: Worldwide Product Safety	3. Report source. (check all that apply)
4. Date received by manufacturer (mm/dd/yyyy)	<input checked="" type="checkbox"/> foreign
01/09/2006	<input checked="" type="checkbox"/> study
6. If IND, protocol #	<input type="checkbox"/> literature
0160003	<input type="checkbox"/> consumer
7. Type of report	<input checked="" type="checkbox"/> health professional
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day	<input type="checkbox"/> user facility
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic	<input type="checkbox"/> company representative
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial	<input type="checkbox"/> distributor
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up# 4	<input type="checkbox"/> other:
5. (A)NDA #	9. Mfr. report number
IND # 58915	WAES 0512DEU00091
8. Adverse event term(s)	
LYMPH NODE ABSCESS; LYMPHANGITIS	

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

non-serious events: hypothyroidism (on 28-SEP-2005 and 18-NOV-2005), hypertriglyceridemia (on 12-OCT-2005), lymphopenia (on 12-OCT-2005), leukopenia and neutropenia (on 03-NOV-2005).

On 25-NOV-2005, the patient developed an abscess of right upper leg (recorded as NSAE).

On 27-NOV-2005, the patient developed a painful swollen lymph node in right groin (5x2 cm) with slight fever. There was no response to a one week antibiotic treatment with clindamycin 300 mg three times a day PO from 05-DEC-2005 until 15-DEC-2005. Ultrasound of lymph nodes could not clearly differentiate between "reactive" or lymphoma manifestation.

Therefore, the patient was hospitalized on 15-DEC-2005 for diagnostic lymph node excision. Result: lymph node abscess with draining of pus; detection of Staphylococcus aureus resistant to clindamycin. On 15-DEC-2005, therapy with 2.2 g amoxicillin (+) clavulanate potassium (AUGMENTAN) and 500 mg ciprofloxacin hydrochloride (CIPROBAY) was started. Diagnosis was bacterial lymph node abscess. Therapy with vorinostat continued. On 20-DEC-2005, outcome was reported as recovered.

On 21-DEC-2005, the patient developed lymphangitis of right upper leg. The same day, therapy with study medication was interrupted. The patient recovered and was discharged on 27-DEC-2005. On 04-JAN-2006, study therapy was restarted.

The investigator felt that bacterial lymph node abscess and lymphangitis of right upper leg were possibly related to study therapy (vorinostat or bexarotene).

Lymphangitis of right upper leg prolonged hospitalization. Additional information is not expected.

This is an amended report. The onset date of "Lymph node abscess" was changed to 15-DEC-2005.

This is a corrected report, as amended.

6. Relevant tests/laboratory data, including dates

DIAGNOSTIC TEST

Tests	Date	Value Unit	Normal Range
ultrasound	12/??/2005		
Comment: could not clearly differentiate between "reactive" or lymphoma manifestation			
diagnostic pathological examination	12/15/2005		
Comment: lymph node abscess with draining of pus; Staphylococcus aureus resistant to clindamycin			

C. Suspect medication(s)

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

#1 CAP vorinostat 100 mg
 #2 CAP bexarotene 75 mg/m²
 #2 CAP bexarotene 75 mg/m²

2. Dose, frequency & route used

#1 200 mg/DAILY/PO
 #2 150 mg/m²/DAILY/PO
 #2 150 mg/m²/DAILY/PO

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

#1 01/04/2006 - Cont
 #2 09/28/2005 - 12/21/2005
 #2 01/04/2006 - Cont

4. Diagnosis for use (indication)

#1 Cutaneous T-cell lymphoma
 #2 Cutaneous T-cell lymphoma
 #2 Cutaneous T-cell lymphoma

5. Event abated after use stopped or dose reduced

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

6. Lot # (if known)

#1
#2
#2

7. Exp date (if known)

#1
#2
#2

8. Event reappeared after reintroduction

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