

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

Page 1

Mfr report #	WAES 0804DEU00125
UF/Dist report #	
	FDA Use Onl

A. Patient information			
1. Patient identifier Confidential AN 2045 in confidence	2. Age at time of event: or 48 years Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight Unk

B. Adverse event or product problem	
<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 checked="" type="checkbox"/> Disability or Permanent Damage
<input checked="" type="checkbox"/> Life-threatening	<input type="checkbox"/> Congenital Anomaly/Birth Defect
<input checked="" type="checkbox"/> Hospitalization-initial or prolonged	<input checked="" 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)	04/16/2008	4. Date of this report (mm/dd/yyyy)	03/06/2009
5. Describe event or problem			

This is in follow-up to report(s) previously submitted on 4/30/2008; 5/2/2008; 5/9/2008; 6/4/2008; 7/8/2008; 7/17/2008; 7/28/2008; 8/20/2008; 9/11/2008; 9/15/2008

Expanded Access Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (SAHA) in Advanced Cutaneous T-cell Lymphoma

Information has been received from an investigator concerning a 48-year-old female patient with thrombocytopenia, tumor-induced anemia and hypothyroidism due to bexarotene therapy and a history of partial pharyngeal excision (due to infiltration of cutaneous T-cell lymphoma) who entered a study, title as stated above.

On 21-MAR-2008, the patient was placed on therapy with vorinostat, 100 mg capsule, 400 mg, once a day for the treatment of cutaneous T-cell lymphoma.

(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: Pharyngeal operation CONCURRENT CONDITIONS: Hypothyroidism; Thrombocytopenia; Anaemia of malignant disease

C. Suspect medication(s)	
1. Name (Give labeled strength & mfr/labeler)	
# 1	CAP vorinostat 100 mg
# 2	

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
# 1 400 mg/DAILY/PO	# 1 03/21/2008 - 04/20/2008
# 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 checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
	# 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 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

9. NDC # or Unique ID	10. Concomitant medical products and therapy dates (excluded treatment of event)
Unknown	Unknown

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)	3. Report source. (check all that apply)
09/04/2008	<input checked="" type="checkbox"/> foreign <input checked="" type="checkbox"/> study <input type="checkbox"/> literature <input type="checkbox"/> consumer health professional <input type="checkbox"/> user facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other
5. (A)NDA # 21991 IND # 58915 STN # PMA/ 510(k) #	
6. If IND, protocol #	
0420012	
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# 10	
9. Mfr. report number	
WAES 0804DEU00125	

8. Adverse event term(s)
HYPERCALCAEMIA; T-CELL LYMPHOMA; BONE METABOLISM DISORDER; RENAL IMPAIRMENT; THROMBOCYTOPENIA; CANDIDA SEPSIS; STAPHYLOCOCCAL SEPSIS; PNEUMONIA

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**

On 16-APR-2008, the patient was hospitalized as an emergency case due to weakness, weight loss, joint pain (since 04-APR-2008) and worsening of thrombocytopenia (platelet count that day was 66 G/l, thrombocytopenia grade 4). Upon admission, physical examination showed exulcerated tumor nodes and ubiquitous papules over the entire integument, marked, mobile indolent infiltrates and lymph node enlargements at all lymph node stations. Lymph node ultrasound showed lymph node enlargements at all stations typical of lymphoma. ECG revealed no pathological finding. That same day, laboratory analysis revealed serum calcium 3.5 mmol/l, serum creatinine 1.3 mg/dl and serum blood urea 61 mg/dl; the patient was diagnosed with hypercalcemia (not yet life-threatening) and renal insufficiency (grade 2 CTCAE, dialysis was not necessary).

On 18-APR-2008, radionuclear bone scan showed joint enhancements; diagnosis was increased bone metabolism in joints. CT showed paraaortal lymph nodes as well as all other lymphatic areas involved; diagnosis was worsening of cutaneous T-cell lymphoma. The initial staging with CT, radionuclear bone scan, biopsies and lymph node ultrasound revealed a significant progress with osseous involvement of the lymphoma. Laboratory analysis revealed serum calcium 3.3 mmol/l, serum blood urea 74 mg/dl and platelet count 64 G/l. On 20-APR-2008, study therapy was discontinued.

On 21-APR-2008, due to her hypercalemia the patient developd clouding of consciousness and then coma and was transferred to ICU, with fever (38.6°C) and increased heart rate. Laboratory analysis revealed serum creatinine 1.7 mg/dl, serum blood urea 97 mg/dl, platelet count 14 G/l and 80 G/l and serum calcium 4.7 mmol/l at 11:52 am and 4.5 mmol/l at 21:24 pm (hypercalcemia was now considered as life-threatening). Chest X-ray showed dyselectases and/or beginning dyselectatic infiltrates, heart slightly dilated with moderate congestion. Under forced diuresis and pamidroinc acid infusions the patient's hypercalcemia improved (serum calcium decreased (no longer life-threatening). On 22-APR-2008, laboratory analysis revealed serum blood urea 112 mg/dl. On 23-APR-2008, laboratory analysis revealed serum calcium 3.7 mmol/l, serum creatinine 1.9 mg/dl and serum blood urea 123 mg/dl. That same day, therapy with liposomal doxorubin (CAELYX) was initiated (20 mg/m² body surface) which was well tolerated. On 24-APR-2008, laboratory analysis revealed serum calcium 3.0 mmol/l and 3.3 mmol/l, serum creatinine 1.9 mg/dl and serum blood urea 116 mg/dl.

On 25-APR-2008, the patient was transferred to the normal ward. Laboratory analysis revealed serum calcium 2.8 mmol/l. On 26-APR-2008, the patient recovered from renal impairment and hypercalemia (serum calcium 2.5 mmol/l) but worsening of cutaneous T-cell lymphoma persisted. On 28-APR-2008, the patient developed significant deterioration of her general condition. Secondary finding was bursitis of elbow. Due to massive saline infusion therapy, the patient developed a transitory hypocalcemia (serum calcium 1.9 mmol/l) at the end of April 2008. On 29-APR-2008, laboratory analysis revealed increase of liver enzymes (values not reported). The patient's general condition was stable.

On 03-MAY-2008, the patient developed chills. That same day, she was diagnosed with candida sepsis due to central venous catheter (since stay in ICU). She was treated with piperacillin/sulbactam sodium/cefazolin and, in the further course, with meropenem/levofloxacin and fluconazole. The patient also developed oral candidiasis which was treated with amphotericin B. On 04-MAY-2008, the patient developed fever (40°C). On 08-MAY-2008, the patient was started on therapy with doxorubicin (20 mg/m² body surface), and received 4 cycles altogether. Due to this therapy, the patient developed stomatitis with initial detection of herpes simplex virus 1 and she was treated with acyclovir IV. Concomitantly, the patient received adjuvant systemic PUVA therapy up to a dosage of 1 J/cm² four times a week. On 12-MAY-2008, chest X-ray showed pleural effusion with compression of basal lung sections. On 13-MAY-2008, lymph node ultrasound showed still large axillary and inguinal lymph nodes (up to 35.9 mm). That same day, the patient recovered from candida sepsis. On 15-MAY-2008, ECG revealed no pathological finding.

On 31-MAY-2008, the patient developed fulminant staphylococcus sepsis and pneumonia requiring catecholamine treatment. The patient was again transferred to ICU. She was treated with piperacillin sodium (+) tazobactam sodium and fluconazole. Chest X-ray showed no congestion, no pneumothorax. That same day, chest X-ray showed increasing congestion. ECG showed sinus tachycardia and ventricular extrasystoles. On 01-JUN-2008, CT showed bilateral pneumonia, splenic infarction (NSAE), regressive lymphoma involvement. Head CT showed no pathological finding. On 02-JUN-2008, the patient developed leukopenia. On 03-JUN-2008, chest X-ray showed pneumonic infiltrates. On 06-JUN-2008, the patient was restransferred to the normal ward. Therapy was changed to piperacillin/sulbactam sodium and fluconazole.

The patient received again chemotherapy with doxorubicin which led to worsening of stomatitis causing impairment of food intake. She received high-calorie diet and temporary parenteral feeding but weight loss continued. On 10-JUN-2008, chest X-ray showed right pneumonic infiltrates decreased, mild left pleural effusion. On 16-JUN-2008, the patient recovered from staphylococcus sepsis and pneumonia. On 18-JUN-2008, the patient was started on therapy with interferon alpha-2a (initially 3 million IU 3 times a week, thereafter increased to 6 million IU three times a week). In the further course, the patient's general condition markedly stabilized. Diagnostic imaging

showed regression of lymph nodes. On 02-JUL-2008, the patient received pamidronate disodium 15 mg due to hypercalcemia.

On 04-JUL-2008, the patient underwent excision of tumor nodes from left lower leg and both upper arms under local anesthesia. Histologic examination revealed pleomorphic advanced CTCL (upper arms), mycosis fungoides (lower leg). That same day, the patient was discharged from hospital in a stable condition, considering the circumstances, and as recovered from worsening of cutaneous T-cell lymphoma, worsening of thrombocytopenia, increased bone metabolism in joints. Outpatient treatment with doxorubicin infusion was planned for 10-JUL-2008. Recommended treatment included systemic PUVA (three times a week), antibiotic therapy with fluconazole and clarithromycin and reduction of systemic corticosteroids according to findings.

The reporting investigator felt that hypercalcemia, increased bone metabolism in joints and renal impairment were probably related to study therapy; he felt that worsening of cutaneous T-cell lymphoma and worsening of thrombocytopenia were probably not related to study therapy and that candida sepsis, staphylococcal sepsis and pneumonia were definitively not.

Hypercalcemia, worsening of thrombocytopenia, candida sepsis, staphylococcal sepsis and pneumonia were considered to be immediately life-threatening. Hypercalcemia and worsening of thrombocytopenia were considered to be disabling. Increased bone metabolism in joints and renal impairment were considered to be other important medical events.

Additional information has been requested.

This is an amended report. The subenvironment was changed from MRL-non-IND to Compassionate Use.

This is corrected as amended.

6. Relevant tests/laboratory data, including dates

DIAGNOSTIC TEST

<u>Tests</u>	<u>Date</u>	<u>Value Unit</u>	<u>Normal Range</u>
ultrasound Comment: lymph node enlargements at all stations typical of lymphoma	04/16/2008		
electrocardiogram Comment: no pathological finding	04/16/2008		
physical examination Comment: exulcerated tumor nodes and ubiquitous papules over the entire integument, marked, mobile indolent	04/16/2008		
radionuclear scan Comment: joint enhancements	04/18/2008		
computed axial tomography Comment: paraaortal lymph nodes as well as all other lymphatic areas involved	04/18/2008		
chest X-ray Comment: dyselectases and/or beginning dyselectatic infiltrates, heart slightly dilated with moderate congest	04/21/2008		
chest X-ray Comment: pleural effusion with compression of basal lung sections	05/12/2008		
ultrasound Comment: still large axillary and inguinal lymph nodes (up to 35.9 mm)	05/13/2008		
electrocardiogram Comment: no pathological finding	05/15/2008		
chest X-ray Comment: no congestion, no pneumothorax	05/31/2008		
electrocardiogram Comment: sinus tachycardia and ventricular extrasystoles	05/31/2008		
chest X-ray Comment: increasing congestion	05/31/2008		
computed axial tomography Comment: bilateral pneumonia, splenic infarction, regressive lymphoma involvement	06/01/2008		
head computed axial tomography Comment: no pathological finding	06/01/2008		
chest X-ray Comment: pneumonic infiltrates	06/03/2008		
chest X-ray Comment: right pneumonic infiltrates decreased, mild left pleural effusion	06/10/2008		
diagnostic radiology	06/??/2008		

Comment: regression of lymph nodes

diagnostic pathological examination

07/04/2008

Comment: pleomorphic advanced CTCL (upper arms), mycosis fungoides (lower leg)

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u>	<u>Unit</u>	<u>Normal Range</u>
platelet count	04/16/2008	66	G/l	150 - 400
serum blood urea	04/16/2008	51	mg/dl	- 50
serum calcium	04/16/2008	3.5	mmol/l	2.15 - 2.55
serum creatinine	04/16/2008	1.3	mg/dl	0.5 - 0.9
platelet count	04/18/2008	64	G/l	150 - 400
serum blood urea	04/18/2008	74	mg/dl	- 50
serum calcium	04/18/2008	3.3	mmol/l	2.15 - 2.55
platelet count	04/21/2008	80	G/l	150 - 400
platelet count	04/21/2008	14	G/l	150 - 400
serum blood urea	04/21/2008	97	mg/dl	- 50
serum calcium	04/21/2008	4.9	mmol/l	2.15 - 2.55
serum calcium	04/21/2008	4.5	mmol/l	2.15 - 2.55
serum creatinine	04/21/2008	1.7	mg/dl	0.5 - 0.9
serum blood urea	04/22/2008	112	mg/dl	- 50
serum blood urea	04/23/2008	123	mg/dl	- 50
serum calcium	04/23/2008	3.7	mmol/l	2.15 - 2.55
serum creatinine	04/23/2008	1.7	mg/dl	0.5 - 0.9
serum blood urea	04/24/2008	116	mg/dl	- 50
serum calcium	04/24/2008	3.0	mmol/l	2.15 - 2.55
serum calcium	04/24/2008	3.3	mmol/l	2.15 - 2.55
serum creatinine	04/24/2008	1.9	mg/dl	0.5 - 0.9
serum calcium	04/??/2008	1.9	mmol/l	2.15 - 2.55
serum calcium	04/25/2008	2.8	mmol/l	2.15 - 2.55
serum calcium	04/26/2008	2.5	mmol/l	2.15 - 2.55
hepatic function tests	04/29/2008			

Comment: liver enzymes increased