

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 0801USA00431
UF/Dist report #	
FDA Use On	

A. Patient information			
1. Patient identifier Unk AN 02863 in confidence	2. Age at time of event: or 54 years Date of Birth: 01/31/1953	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 101 lbs

B. Adverse event or product problem	
1. <input checked="" type="checkbox"/> Adverse event and / or (check all that apply)	<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 type="checkbox"/> Life-threatening	<input type="checkbox"/> Congenital Anomaly/Birth Defect
<input 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)	12/31/2007	4. Date of this report (mm/dd/yyyy)	12/03/2008
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5. Describe event or problem
This is in follow-up to report(s) previously submitted on 1/11/2008; 2/11/2008; 2/21/2008; 4/4/2008

A Randomized Phase IIa Study of Vorinostat in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes

Information has been received from an investigator concerning a 54 year old black female with anaemia, fatigue, genital lesion, sore throat, perineal infection, and thrombocytopenia and a history of headache, hysterectomy, anorexia, chills, chronic lower back pain, weight loss, and night sweats who entered a study, title as stated above. On 06-NOV-2007, the patient was randomized. On 06-NOV-2007 through 12-NOV-2007, and 15-NOV-2007 through 19-NOV-2007, the patient received cycle 1 therapy with vorinostat, capsule, 200 mg, three times a day for 14/21 days for the treatment of myelodysplastic syndrome (total dose given 6400). On 04-DEC-2007 through 17-DEC-2007, the patient received cycle 2 of therapy with vorinostat capsule 200 mg three

(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: Headache; Hysterectomy; Anorexia; Weight decreased; Night sweats; Chronic back pain; Chills

CONCURRENT CONDITIONS: Anaemia; Fatigue; Genital lesion; Sore throat; Thrombocytopenia; Perineal infection

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)
# 1 200 mg/TID/PO	# 1 11/06/2007 - 11/12/2007
# 2	# 2

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced.
# 1 Myelodysplastic syndrome	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
Unknown

10. Concomitant medical products and therapy dates (excluded treatment of event)	
BENADRYL	10/??/2007 - Cont
COMPazine	11/06/2007 - 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: World Wide Product Safety	(215) 652-8071
3. Report source (check all that apply)	
<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	

4. Date received by manufacturer (mm/dd/yyyy)	5. (A)NDA # 21991 IND # 58915
11/24/2008	

6. If IND, protocol #	7. Type of report
0640004	<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# 4

8. Adverse event term(s)	9. Mfr report number
NEUROPATHY	WAES 0801USA00431

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**

time a day (total dose given 8,400). On 25-DEC-2007 through 31-DEC-2007, the patient received cycle 3 study therapy with vorinostat 200 mg three times a day (total dose given 4,300). Concomitant therapy included acetaminophen (TYLENOL), diphenhydramine HCl (BENADRYL), prochlorperazine maleate (COMPAZINE), ondansetron, valacyclovir HCl, nystatin, magnesia [milk of], oxycodone, and cephalexin.

On 31-DEC-2007, cycle 3, day 7 of vorinostat 200 mg TID, the patient presented to the outpatient clinic with new onset of peripheral neuropathy, grade 3, in the lower extremities and finger tips. The patient complained of falling the previous day and could not "feel the ground" when ambulating. Physical exam revealed diminished sensation in the lower extremities. On 31-DEC-2007, vorinostat was discontinued.

On 07-JAN-2008, the patient had a hemoglobin of 8.1 and was transfused with packed red cells. The patient returned to the clinic on 07-JAN-2008 and presented with persistent numbness in the lower extremities, but no more events of falling or unsteady gait. The patient returned for follow-up on 15-JAN-2008 with grade 2 neuropathy, but no more episodes of falling. The patient was scheduled to have a neurology consult on 15-FEB-2008. On 28-JAN-2008, the patient was off study due to persistent grade 2 neuropathy.

While vorinostat was held, the neuropathy improved from grade 3 to grade 2. The patient did not return to baseline. Grade 3 to Grade 2 because the patient has had no more episodes of falling. Numbness and tingling remained in the finger tips and soles of her feet with decreased light sensation.

Follow-up plan includes neurology consult on 15-FEB-2008. Continue to monitor neuropathy at weekly visits. The patient is off-study. Blood products transfused as needed for supportive care.

At the time of reporting, the outcome of the neuropathy was not recovered. The investigator felt that the neuropathy was related to study therapy and not related to other therapies.

The investigator felt that the grade 3 neuropathy was disabling.

Follow-up information was received from the investigator. The patient's grade 2 neuropathy never resolved to grade 1 and on 28-JAN-2008, the patient was discontinued from the study due to persistent grade 2 neuropathy.

No additional information is expected.

6. Relevant tests/laboratory data, including dates**DIAGNOSTIC TEST**

<u>Tests</u>	<u>Date</u>	<u>Value</u> <u>Unit</u>	<u>Normal Range</u>
electrocardiogram Comment: result not reported	10/25/2007		
electrocardiogram Comment: result not reported	11/12/2007		
electrocardiogram Comment: result not reported	12/10/2007		

LABORATORY RESULTS

<u>Tests</u>	<u>Date</u>	<u>Value</u> <u>Unit</u>	<u>Normal Range</u>
hemoglobin	01/07/2008	8.1	

C. Suspect medication(s)**1. Name (Give labeled strength & mfr/labeler)**

#1 CAP vorinostat Unk
#1 CAP vorinostat Unk
#1 CAP vorinostat Unk

2. Dose, frequency & route used

#1 200 mg/TID/PO
#1 200 mg/TID/PO
#1 200 mg/TID/PO

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

#1 11/15/2007 - 11/19/2007
 #1 12/04/2007 - 12/17/2007
 #1 12/25/2007 - 12/31/2007

4. Diagnosis for use (indication)

#1 Myelodysplastic syndrome
 #1 Myelodysplastic syndrome
 #1 Myelodysplastic syndrome

5. Event abated after use stopped or dose reduced

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

6. Lot # (if known)

#1
 #1
 #1

7. Exp date (if known)

#1
 #1
 #1

8. Event reappeared after reintroduction

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

C. Suspect medication(s)

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

TYLENOL	10/??/2007 - Cont
cephalexin	12/24/2007 - 01/14/2008
magnesia [milk of]	12/03/2007 - Cont
nystatin	11/13/2007 - Cont
ondansetron	11/07/2007 - Cont
oxycodone	12/13/2007 - Cont
valacyclovir hydrochloride	12/13/2007 - 12/23/2007