



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: January 9, 2009

To: NCCTG Primary Clinical Research Associates

From: Janis Wobschall

Re: N0776, Phase II Trial of Avastin® in Combination with Sorafenib in Recurrent Glioblastoma Multiforme

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with Bevacizumab for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_556768_F1

Please note that all risks currently cited in the NCCTG consent form cannot be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Janis Wobschall at wobschall.janis@mayo.edu or 507-284-4852.

JW/kjm
enclosure



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: November 4, 2008

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
Igor Espinoza-Delgado, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: Bevacizumab (rhuMab VEGF) and Rituxamab Investigator Notification: **Hemoptysis**
Genentech Manufacturer Report # 556768

TO: Investigators using Bevacizumab (NSC 704865) or Rituximab (NSC 687451)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. A MedWatch report and CIOMS form, which describe hemoptysis in a patient participating in a Genentech-sponsored clinical trial utilizing the investigational agent bevacizumab in combination with rituximab and chemotherapy, was recently distributed to investigators.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460 and rituximab under NCI INDs 7028 and 10624:

- Send a copy of this letter to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of this letter in your protocol file.

If your study is not covered under INDs 7028, 7921, 10624, or 11460, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with bevacizumab and rituximab, there does not appear to be a change in the risk-benefit ratio for bevacizumab or rituximab studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The MedWatch Report and CIOMS Form that describe the following adverse event are attached:

A 55-year-old female with CD20-positive diffuse large B-cell lymphoma experienced fatal hemoptysis while on a phase 3 study utilizing the investigational agent bevacizumab in combination with rituximab and chemotherapy.

Attachments: MedWatch Report
CIOMS Form

MEDWATCH

For use by user-facilities,
distributors and manufacturers for
MANDATORY reporting.

258964

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of 3

Mfr report #	556768
DF/Importer report #	
FDA Use only	

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at time of event: or 55 YEARS Date of birth:	3. Sex <input checked="" type="checkbox"/> female <input type="checkbox"/> male	4. Weight 141.1 lbs or 64 kgs
In confidence			

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 03/ 31 /2008 <input type="checkbox"/> life threatening <input type="checkbox"/> hospitalization-initial or prolonged <input type="checkbox"/> disability or permanent damage	<input type="checkbox"/> congenital anomaly/birth defect <input type="checkbox"/> required intervention to prevent permanent impairment/damage (devices) <input type="checkbox"/> other serious (important medical events)
3. Date of event (mm/dd/yyyy) 03/ 31 /2008	4. Date of this report (mm/dd/yyyy) 10/ 13 /2008

5. Describe event or problem
BO20603
MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III TRIAL COMPARING THE EFFICACY OF BEVACIZUMAB IN COMBINATION WITH RITUXIMAB AND CHOP (RA-CHOP) VERSUS RITUXIMAB AND CHOP (R-CHOP) IN PREVIOUSLY UNTREATED PATIENTS WITH CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL).

A 55-YEAR-OLD FEMALE PATIENT DIED OF ACTIVE HEMOPTYSIS DURING PARTICIPATION IN THE ABOVE STUDY.

ON 12 MARCH THE PATIENT REPORTED AN IMPROVEMENT IN HER DISEASE, LESS PAIN AND HER COUGHING ALMOST DISAPPEARING. ON 14 MARCH 2008, INTRAVENOUS (IV) BLINDED BEVACIZUMAB WAS STARTED. THE FOLLOWING DAY, IV RITUXIMAB (375 MG/M2, ONCE EVERY THREE WEEKS), IV CYCLOPHOSPHAMIDE (750 MG/M2, ONCE EVERY THREE WEEKS), IV VINCRIStINE (1 MG/M2, ONCE EVERY THREE WEEKS), IV DOXORUBICIN (50 MG/M2, ONCE EVERY THREE WEEKS) AND ORAL PREDNISONE (100 MG

CONTINUED

6. Relevant tests/laboratory data, including dates
UNK

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Medical History Terms
DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0
NON-HODGKIN'S LYMPHOMA/NON-HODGKIN'S LYMPHOMA/MEDDRA 11.0 31-MAR-2008

C. SUSPECT PRODUCT(S)

1. Name (give labeled strength & mfr/labeler) #1 BEVACIZUMAB (BEVACIZUMAB) #2 RITUXIMAB (RITUXIMAB)	
2. Dose, frequency & route #1 15 MG/KG 1 per 3 WEEK INTRAVENOUS #2 375 MG/M2 1 per 3 WEEK INTRAVENOUS	3. Therapy dates (if unk. give duration) from/to (or best estimate) #1 14-MAR-2008 / 14-MAR-2008 #2 15-MAR-2008 / 15-MAR-2008
4. Diagnosis for use (indication) #1 DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0 #2 DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0	5. Event abated after use stopped or dose reduced #1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply #2 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply
6. Lot # #1 See attached #2 UNK	7. Exp. date #1 UNK #2 UNK
8. NDC # or Unique ID #1 NA #2 NA	9. Event reappeared after reintroduction #1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply #2 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply
10. Concomitant medical products and therapy dates (exclude treatment of event) UNK	

G. ALL MANUFACTURERS

1. Contact Office-name/address (& mfring site for devices)	2. Phone Number
3. Report source (check all that apply) <input checked="" 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) 10/ 03 /2008	6. (A)NDA# IND # STN # PMA#10(k)# Combination product <input type="checkbox"/> yes pre-1938 <input type="checkbox"/> yes OTC product <input type="checkbox"/> yes
5. If IND, protocol # BO20603	7. Type of report (check all that apply) <input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> 7-day <input type="checkbox"/> periodic <input type="checkbox"/> 10-day <input type="checkbox"/> 30-day <input type="checkbox"/> initial <input checked="" type="checkbox"/> follow-up # 1
8. MFR. report number 556768	9. Adverse event term(s) ACTIVE HEMOPTYSIS/HAEMOPTYSIS/MEDDRA 11.0 +++ +++ adverse event that generated submission

E. INITIAL REPORTER

1. Name, address	Phone #
2. Health professional? <input checked="" type="checkbox"/> yes <input type="checkbox"/> no	3. Occupation DOCTOR OF MEDICINE
4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> unk	

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11/13/2008

GENERAL DRUG SAFETY



Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

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B.5. Describe event or problem - continued

GIVEN DAYS 1-5 OF THREE WEEK CYCLE) WERE STARTED. APPROXIMATELY ELEVEN DAYS LATER, ON 26 MARCH 2008, SHE COMPLAINED OF A DRY COUGH AGAIN AND WAS ADVISED TO VISIT THE OUTPATIENT CLINIC, HOWEVER SHE DID NOT ARRIVE. TWO DAYS LATER, SHE COMPLAINED OF CHEST PAIN AND WAS AGAIN ADVISED TO GO TO THE CLINICAL; AGAIN SHE DID NOT ARRIVE. ON 29 MARCH 2008, THE PATIENT WAS ADMITTED TO HOSPITAL DUE TO RESPIRATORY INSUFFICIENCY, FEVER, COUGH, PHLEGM AND SUDDEN CARDIOVASCULAR FAILURE. SHE EXPERIENCED HAEMOPTYSIS AND WAS TRANSFUSED WITH ONE UNIT OF BLOOD. NO ACTION WAS TAKEN WITH STUDY THERAPY, WHICH WAS ONGOING AT THE TIME OF DEATH.

THE INVESTIGATOR ASSESSED THE EVENT AS NOT RELATED TO RITUXIMAB AND BLINDED BEVACIZUMAB AS SHE IMPROVED CLINICALLY SOON AFTER THE TREATMENT WAS ADMINISTERED BUT AS POSSIBLY RELATED TO LYMPHOMA NON-HODGKIN. NO OTHER INFORMATION WAS AVAILABLE.

THE DRUG CODE WAS BROKEN DUE TO REGULATORY REQUIREMENTS ON 08 APRIL 2008. THE PATIENT RECEIVED BEVACIZUMAB (15 MG/KG, ONCE EVERY THREE WEEKS).

UPDATE INFORMATION WAS RECEIVED AND THE FOLLOWING WAS ADDED TO THE CASE: THE CAUSE OF DEATH HAS BEEN PROVIDED.

C.1. thru C.9. Suspect medication(s) - continued

Suspect medication #1

C6. Lot # (if known)
14040, 14376, 11395

Suspect medication #3

C.1. Name and Strength (give mfr/labeler, if known)
CYCLOPHOSPHAMIDE (CYCLOPHOSPHAMIDE)

C.2. Dose, frequency and route
750 MG/M2 1 per 3 WEEK INTRAVENOUS

C.3. Therapy dates (if unk. give duration) from/to or best estimate
15-MAR-2008 / 15-MAR-2008

C.4. Diagnosis for use (indication)
DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0

C.5. Event abated after use stopped or dose reduced
DOESN'T APPLY

C.6. Lot # (if known)
UNK

C.7. Exp. date
UNK

C.8. Event reappeared after reintroduction
DOESN'T APPLY

C.9. NDC # - for product problems only
NA

Suspect medication #4

C.1. Name and Strength (give mfr/labeler, if known)
VINCRISTINE (VINCRISTINE)

C.2. Dose, frequency and route
1 MG/M2 1 per 3 WEEK INTRAVENOUS

C.3. Therapy dates (if unk. give duration) from/to or best estimate
15-MAR-2008 / 15-MAR-2008

C.4. Diagnosis for use (indication)
DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0

C.5. Event abated after use stopped or dose reduced
DOESN'T APPLY

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C.6. Lot # (if known)
UNK

C.7. Exp. date
UNK

C.8. Event reappeared after reintroduction
DOESN'T APPLY

C.9. NDC # - for product problems only
NA

Suspect medication #5

C.1. Name and Strength (give mfr/labeler, if known)
DOXORUBICIN (DOXORUBICIN)

C.2. Dose, frequency and route
50 MG/M2 1 per 3 WEEK INTRAVENOUS

C.3. Therapy dates (if unk. give duration) from/to or best estimate
15-MAR-2008 / 15-MAR-2008

C.4. Diagnosis for use (indication)
DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0

C.5. Event abated after use stopped or dose reduced
DOESN'T APPLY

C.6. Lot # (if known)
UNK

C.7. Exp. date
UNK

C.8. Event reappeared after reintroduction
DOESN'T APPLY

C.9. NDC # - for product problems only
NA

Suspect medication #6

C.1. Name and Strength (give mfr/labeler, if known)
PREDNISONE (PREDNISONE) 50 MG

C.2. Dose, frequency and route
60 MG/M2 5 per 3 WEEK ORAL

C.3. Therapy dates (if unk. give duration) from/to or best estimate
15-MAR-2008 / 20-MAR-2008

C.4. Diagnosis for use (indication)
DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0

C.5. Event abated after use stopped or dose reduced
DOESN'T APPLY

C.6. Lot # (if known)
UNK

C.7. Exp. date
UNK

C.8. Event reappeared after reintroduction
DOESN'T APPLY

C.9. NDC # - for product problems only
NA

E.1. Initial reporter (Name, address & phone #) - continued

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SUSPECT ADVERSE EVENT REPORT

EVENT INFORMATION

PAGE 1 OF 3

1. PATIENT INITIALS (FIRST, LAST) (IN CONFIDENCE)	1A. COUNTRY	2. DATE OF BIRTH			2A. AGE (YRS) 55 YR	3. SEX F	4-6. EVENT ONSET			8-12. CHECK ALL APPROPRIATE
		DA	MO	YR			DA	MO	YR	
7. DESCRIBE REACTIONS INCLUDING RELEVANT TESTS/LAB DATA							<input checked="" type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION <input type="checkbox"/> INVOLVED SIGNIFICANT DISABILITY OR INCAPACITY? <input type="checkbox"/> LIFE THREATENING			
2006-005520-16. B020603 MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III TRIAL COMPARING THE EFFICACY OF BEVACIZUMAB IN COMBINATION WITH RITUXIMAB AND CHOP (RA-CHOP) VERSUS RITUXIMAB AND CHOP (R-CHOP) IN PREVIOUSLY UNTREATED PATIENTS WITH CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL). A 55-YEAR-OLD FEMALE PATIENT DIED OF ACTIVE HEMOPTYSIS DURING PARTICIPATION IN THE ABOVE STUDY. ON 12 MARCH THE PATIENT REPORTED AN IMPROVEMENT IN HER DISEASE, LESS PAIN AND HER COUGHING ALMOST DISAPPEARING. ON 14 MARCH 2008, INTRAVENOUS (IV) BLINDED BEVACIZUMAB WAS STARTED. THE FOLLOWING DAY, IV RITUXIMAB (375 MG/M2, ONCE EVERY THREE WEEKS), IV CYCLOPHOSPHAMIDE (750 MG/M2, ONCE EVERY THREE WEEKS), IV VINCRIStINE (1 MG/M2, ONCE EVERY THREE WEEKS), IV DOXORUBICIN (50 MG/M2, ONCE							CONTINUED			

SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUGS (INCLUDE GENERIC NAME) BEVACIZUMAB (BEVACIZUMAB)		20. DID EVENT ABATE AFTER STOPPING DRUGS? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA	
15. DAILY DOSE(S) / STRENGTH 15 MG/KG 1 X per 3 WEEK /		16. ROUTE(S) OF ADMINISTRATION INTRAVENOUS	
17. INDICATION(S) FOR USE DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0		21. DID EVENT REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA	
18. THERAPY DATES (FROM/TO) FROM 14-MAR-2008 TO 14-MAR-2008		19. THERAPY DURATION .1 DAYS	

CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (EXCLUDE THOSE USED TO TREAT EVENT)	
23. OTHER RELEVANT HISTORY (E.G. DIAGNOSES, ALLERGIES, PREGNANCY, WITH LMP, ETC.) MEDICAL HISTORY TERM(S): DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0 NON-HODGKIN'S LYMPHOMA/NON-HODGKIN'S LYMPHOMA/MEDDRA 11.0	

MANUFACTURER INFORMATION

24. NAME AND ADDRESS OF MANUFACTURER	
24b. MFR. CONTROL NO. 556768	
24c. DATE RECEIVED BY MANUFACTURER 3-OCT-2008	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL
25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP	

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Where MedDRA is used the following format applies: Reported term/ MedDRA LLT/version number

7. DESCRIBE REACTIONS INCLUDING RELEVANT TESTS/LAB DATA - continued

EVERY THREE WEEKS) AND ORAL PREDNISONE (100 MG GIVEN DAYS 1-5 OF THREE WEEK CYCLE) WERE STARTED. APPROXIMATELY ELEVEN DAYS LATER, ON 26 MARCH 2008, SHE COMPLAINED OF A DRY COUGH AGAIN AND WAS ADVISED TO VISIT THE OUTPATIENT CLINIC, HOWEVER SHE DID NOT ARRIVE. TWO DAYS LATER, SHE COMPLAINED OF CHEST PAIN AND WAS AGAIN ADVISED TO GO TO THE CLINICAL; AGAIN SHE DID NOT ARRIVE. ON 29 MARCH 2008, THE PATIENT WAS ADMITTED TO HOSPITAL DUE TO RESPIRATORY INSUFFICIENCY, FEVER, COUGH, PHLEGM AND SUDDEN CARDIOVASCULAR FAILURE. SHE EXPERIENCED HAEMOPTYSIS AND WAS TRANSFUSED WITH ONE UNIT OF BLOOD. NO ACTION WAS TAKEN WITH STUDY THERAPY, WHICH WAS ONGOING AT THE TIME OF DEATH. THE INVESTIGATOR ASSESSED THE EVENT AS NOT RELATED TO RITUXIMAB AND BLINDED BEVACIZUMAB AS SHE IMPROVED CLINICALLY SOON AFTER THE TREATMENT WAS ADMINISTERED BUT AS POSSIBLY RELATED TO LYMPHOMA NON-HODGKIN.

NO OTHER INFORMATION WAS AVAILABLE.

THE DRUG CODE WAS BROKEN DUE TO REGULATORY REQUIREMENTS ON 08 APRIL 2008. THE PATIENT RECEIVED BEVACIZUMAB (15 MG/KG, ONCE EVERY THREE WEEKS).

UPDATE INFORMATION WAS RECEIVED AND THE FOLLOWING WAS ADDED TO THE CASE: THE CAUSE OF DEATH HAS BEEN PROVIDED.

ADVERSE EVENT TERM(S):

ACTIVE HEMOPTYSIS/HEMOPTYSIS/MEDDRA 11.0 +++

(+++ denotes adverse event that generated submission)

14-19. SUSPECT DRUGS - continued

Suspect Drug: RITUXIMAB
 Generic Name: RITUXIMAB
 Daily Dose(s)/Strength: 375 MG/M2 1 X per 3 WEEK /
 Route: INTRAVENOUS
 Indication: DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0
 Therapy From Date: 15-MAR-2008
 Therapy To Date: 15-MAR-2008
 Therapy Duration: 1 DAYS

Suspect Drug: CYCLOPHOSPHAMIDE
 Generic Name: CYCLOPHOSPHAMIDE
 Daily Dose(s)/Strength: 750 MG/M2 1 X per 3 WEEK /
 Route: INTRAVENOUS
 Indication: DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0
 Therapy From Date: 15-MAR-2008
 Therapy To Date: 15-MAR-2008
 Therapy Duration: 1 DAYS

Suspect Drug: VINCRISTINE
 Generic Name: VINCRISTINE
 Daily Dose(s)/Strength: 1 MG/M2 1 X per 3 WEEK /
 Route: INTRAVENOUS
 Indication: DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0
 Therapy From Date: 15-MAR-2008
 Therapy To Date: 15-MAR-2008
 Therapy Duration: 1 DAYS

Suspect Drug: DOXORUBICIN
 Generic Name: DOXORUBICIN
 Daily Dose(s)/Strength: 50 MG/M2 1 X per 3 WEEK /
 Route: INTRAVENOUS
 Indication: DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0
 Therapy From Date: 15-MAR-2008
 Therapy To Date: 15-MAR-2008
 Therapy Duration: 1 DAYS

Suspect Drug: PREDNISONE

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Generic Name: PREDNISONE
Daily Dose(s)/Strength: 60 MG/M2 5 X per 3 WEEK / 50 MG
Route: ORAL
Indication: DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.0
Therapy From Date: 15-MAR-2008
Therapy To Date: 20-MAR-2008
Therapy Duration: 6 DAYS

CIOMS TEXT

A POSSIBLE ALTERNATIVE EXPLANATION FOR THIS FATAL ACTIVE HEMOPTYSIS IN THIS PATIENT RECEIVING BEVACIZUMAB AND RITUXIMAB IS THE PATIENT'S 5) PATIENT'S UNDERLYING DISEASE. BASED UPON THIS SINGLE REPORT, THERE IS NO CHANGE IN THE OVERALL SAFETY PROFILE OF THE PRODUCT.

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