

**MEDWATCH**

FORM FDA 3500A (10/05)

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

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Mfr Report # CA042-09-0165 (0)
UF/Importer Report #
FDA Use Only

<b>A. PATIENT INFORMATION</b>			
1. Patient Identifier E-S In confidence	2. Age at Time of Event 37 Y or Date of Birth: 09/24/1971	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight ____ lbs or 60 kgs

<b>B. ADVERSE EVENT OR PRODUCT PROBLEM</b>	
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 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) 03/16/2009	4. Date of This Report (mm/dd/yyyy) 04/15/2009

5. Describe Event or Problem

A 37 year-old Asian female subject (425/0002) experienced left ventricular systolic dysfunction while enrolled in An Open-Label, Phase II Study of Weekly ABI-007 as First Line Therapy for Patients with Metastatic Breast Cancer. The subject received the first dose of treatment with ABI-007 (100 mg/m2) on 16-Dec-2008. The last dose of ABI-007 (100 mg/m2) received prior to the onset of the serious adverse event was received on 19-Mar-2009.

On 10 February 2009, the subject had an electrocardiogram done prior to surgical repair of a hip fracture. At that time, the heart rate was noted to be 88 beats per minute and some non specific T wave abnormalities were noted. The subject had evidence of sinus tachycardia prior to chemotherapy, with a heart rate of 130 beats per minute. Baseline heart rate prior to cycle 1 of chemotherapy was noted to be 68 beats per minute. Intraoperatively persistent tachycardia was noted as well as episodes of significant desaturation. Computed tomography ruled out embolus. The subject remained tachycardic. On

Cont...

6. Relevant Tests/Laboratory Data, Including Dates

10-Feb-2009 - echocardiogram - normal sinus rhythm at 88 beats per minute with some nonspecific T-wave abnormalities.  
12-Feb-09 - persistent tachycardia noted as well as episodes of significant desaturation.  
(date not provided - computed tomography ruled out embolus.  
09-Mar-2009 -echocardiogram -some minimal voltage changes that might have met the

Cont...

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Concurrent Disease:  
Anxiety[10002855]  
Somnolence[10041349]  
Pathologic fracture of neck of femur[10034136]

<b>C. SUSPECT PRODUCT(S)</b>			
1. Name (Give labeled strength & mfr/labeler) #1 ABI-007 (Abraxane® for Injectable Suspension (paclitaxel) #2 _____ Cont...			
2. Dose, Frequency & Route Used #1 (100 mg/m2, last dose prior to #2 _____		3. Therapy Dates (If unknown, give duration) from/to (or best estimate) #1 12/16/2008 - #2 _____	
4. Diagnosis for Use (Indication) #1 Breast cancer[10006187] #2 _____		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 type="checkbox"/> Doesn't Apply	
6. Lot # #1 _____ #2 _____		7. Exp. Date #1 _____ #2 _____	
8. Event Reappeared After Reintroduction? #1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply #2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply			
9. NDC # or Unique ID UNK			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) 1) DEXAMETHASONE (DEX- 12/21/2008 - ONGOING AMETHASONE) 2) RITALIN (METHYLPHE- 01/20/2009 - NIDATE HYDROCHLORIDE) Cont...			

<b>G. ALL MANUFACTURERS</b>			
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Abraxis BioScience 11755 Wilshire Blvd., Ste 2000 Los Angeles, CA 90025 USA ( Initial Unit )		2. Phone Number Cont...	
4. Date Received by Manufacturer (mm/dd/yyyy) 04/06/2009		5. (A)NDA # IND # 55,974 STN # _____ PMA/ 510(k) # _____ Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # CA042		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:	
7. Type of Report (Check all that apply) <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 checked="" type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> Follow-up # _____		8. Adverse Event Term(s) 1) LEFT VENTRICULAR Cont...	
9. Manufacturer Report Number CA042-09-0165 (0)			

<b>E. INITIAL REPORTER</b>	
1. Name and Address Vanessa Bernstein BC Cancer Agency- Vancouver Island Ctr 2410 Lee Avenue Victoria, BC V8R6V5 CANADA	Phone # (250) 519-5570

2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	3. Occupation Physician	4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unk.
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Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

**B. ADVERSE EVENT OR PRODUCT PROBLEM**

**B.5 Describe Event or Problem (Cont...)**

09-Mar-2009, an echocardiogram was performed because the patient continued to have sinus tachycardia with a ventricular rate of 122 on electrocardiogram. There were some minimal voltage changes that might have met the criteria for left ventricular hypertrophy. Previously the subject was reported to be asymptomatic. On 16-Mar-2009, an echocardiogram was performed which revealed an ejection fraction of 40%. On 26-Mar-2009, a multi gated acquisition scan (MUGA) was notable for a left ventricular ejection fraction of 41%. On 25-Mar-2009, a cardiac consultation was obtained and the subject was treated with bisoprolol. Methylphenidate was discontinued at that time. The subject had been on high doses of dexamethasone (date and dosage not provided) and at the time of the cardiology consult was on 2 mg twice a day. Following therapy with bisoprolol, the subject's heart rate decreased to 88 to 100 beats per minute. The subject's medical history was notable for therapy with anthracyclines from December 2004 to April 2005. Evaluation during the March follow up visits was notable for multiple areas of extensive ground glass appearance in the lungs. Progressive hypoxemia had been noted; on 02 April the subject was noted to have oxygen saturations in the 80's on 3 liters of oxygen and on 03-Apr-2009 oxygen saturations were 75% with ambulation on 4 liters oxygen. At the time of this report, the subject is on 5 L oxygen with a resting oxygen saturation of 97%. A pulmonary consult is pending.

ABI-007 was discontinued on 2-Apr-2009 due to this event.

The subject's medical history was relevant for anxiety, somnolence on 2-Feb-09 (refer to CA042-09-0053) and pathologic fracture on 12-Feb-2009 (refer to CA042-09-0157).

Concomitant medications taken within two weeks of this event included dexamethasone and methylphenidate.

The investigator reported the event of left ventricular systolic dysfunction was possibly related to ABI-007.

**B.6 Relevant Tests/Laboratory Data, Including Dates (Cont...)**

criteria for left ventricular hypertrophy. left ventricular ejection fraction of 40%.  
16-Mar-2009 - echocardiogram - estimated ejection fraction of 40%.  
02-Apr-2009 - oxygen saturation rate in the 80's.  
03-Apr-2009 - oxygen saturation decreased to 75%.

**C. SUSPECT PRODUCT(S) (Cont...)**

Seq No. : 1  
C.1 Suspect Product : ABI-007 (Abraxane® for Injectable Suspension (paclitaxel protein-bound particles) (albumin-bound)) (PACLITAXEL)  
C.2 Dose, Frequency & Route Used : 1) (100 mg/m2, last dose prior to event 19-Mar-2009), Intravenous

**C.10 Concomitant Medical Products and Therapy Dates**

Seq No. : 1  
Concomitant Medical Product : DEXAMETHASONE (DEXAMETHASONE)  
Dose, Frequency & Route Used : 1) 16 mg, Oral  
Diagnosis for Use (Indication) : 1) Nausea [10028813]  
Seq No. : 2  
Concomitant Medical Product : RITALIN (METHYLPHENIDATE HYDROCHLORIDE)  
Diagnosis for Use (Indication) : 1) Somnolence [10041349]

**G. ALL MANUFACTURERS**

**G.2 Phone Number**

(310) 883-1300

**G.8 Adverse Event Term(s)**

1) LEFT VENTRICULAR SYSTOLIC DYSFUNCTION (Left ventricular dysfunction, Left ventricular dysfunction)

**Company Comments:**

**Continuation Sheet for FDA-3500A Form**

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**Date of This Report : 04/15/2009**

Given the development of left ventricular dysfunction following administration of ABI-007, a causal link cannot be ruled out and is possible. Prior therapy with anthracycline, as well as methylphenidate and high dose dexamethasone, all drugs with known cardiotoxicity, may be contributory.

**Analysis of Similar Events:**

A search of the database is notable for seven cases of left ventricular dysfunction, all of which occurred in subjects previously treated with known cardiotoxic agents.

ABILS-06-0281 is a report of a male subject with metastatic breast cancer who experienced congestive heart failure, coincident with receiving Abraxane, and subsequent to therapy with doxorubicin, and cytoxan. The event was deemed unrelated to Abraxane therapy.

ABNYC-06-0364 is a spontaneous report of cardiomyopathy, 23% left ventricular ejection fraction and cardiomegaly regarding a 46 year old female with metastatic breast cancer. After 39 doses of Abraxane, the patient was diagnosed with cardiomyopathy. The patient had previously been treated with anthracycline and was on the concomitant medication cymbalta.

ABX06-06-0174 is a report received from an investigator initiated trial regarding a 74 year old female with metastatic breast cancer who experienced left ventricular dysfunction coincident with Abraxane and Herceptin (trastuzumab) therapy. The consulting cardiologist deemed the event probably related to Herceptin, and the principal investigator deemed the event possibly related to both study drugs. Herceptin therapy was discontinued. Abraxane therapy was restarted and the subject had one additional cardiac event, supraventricular tachycardia, during the remainder of Abraxane therapy.

ABX37-07-0709 is a report received from an investigator initiated trial regarding a 44 year old female with metastatic breast cancer who experienced left ventricular dysfunction coincident with Abraxane, Herceptin (trastuzumab), bevacizumab and carboplatin therapy. The investigator deemed the event related to Herceptin and unrelated to Abraxane.

CA009-05-0296 is a report received from a clinical trial regarding a 56 year old female with metastatic ovarian cancer who experienced left ventricular dysfunction sixty days after her last dose of ABI-007. The subject had progressive disease and co morbid illness at the time of the event, and had been previously treated with cardiotoxic chemotherapeutic agents including doxorubicin.

CA031-09-0088 is a report received from a clinical trial regarding a 60 year old male with advanced non small cell lung cancer who experienced acute left ventricular insufficiency days four months after initiating therapy with ABI-007 and on the same day as an administered dose and coincident with the administration of carboplatin. The subject had a history of coronary artery disease, hypertension and prior evidence of left ventricular hypertrophy.

ABCAS-07-1021 is a spontaneous report of decreased ejection fraction in a female with metastatic breast cancer three months after initiating therapy with Abraxane. The patient had a history of prior therapy with doxorubicin and was receiving the concomitant medication bevacizumab.