Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Oncology Drug Products

Briefing Document

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September 7, 2006
Hilton, Silver Spring, MD

NDA 21-660
Abraxane
Abraxis BioScience, Inc.

DIVISION OF DRUG ONCOLOGY PRODUCTS
ABRAXANE ODAC BRIEFING DOCUMENT
September 7, 2006

NDA:	21-660
Applicant:	Abraxis BioScience, Inc. (ABI)
Drug:	Abraxane (paclitaxel protein-bound particles for injectable suspension). Each 50 mL vial contains 100 mg of paclitaxel and 900 mg of human albumin as a sterile lyophilized powder.

Reviewers:

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Approved Indication: "ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated." The application was approved on January 7, 2005.

Proposed Indication: "ABRAXANE® is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy."

Regulatory Background:

When a marketed drug is off-patent, there are three regulatory pathways for a competitor to bring the drug to market. One is a New Drug Application (NDA) which includes full reports of investigations. A second is an Abbreviated New Drug Application (ANDA) for generic drugs. Abraxane does not qualify for an ANDA because it is not bioequivalent to Taxol. The third is called 505(b)(2), named after section 505 (b)(2) of the Food, Drug and Cosmetic Act which describes it. This applies to new formulations of marketed drugs and authorizes the FDA, **where appropriate**, to base approvals of new drugs entirely or partially on studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Abraxis BioScience Abraxane Proposal:

Abraxis BioScience is proposing the following plan for approval of Abraxane for adjuvant treatment of node positive early breast cancer under section 505(b)(2) of the Food, Drug and Cosmetic Act. The first two bullets are the 505(b)(2) components of the plan. The other components of the plan consist of studies that have been or will be conducted by Abraxis BioScience.

- Results of the randomized Intergroup study that served as the basis for Taxol approval for the adjuvant treatment of node positive early breast cancer.
- Preclinical genetic toxicology studies with Taxol.
- Comparison of the pharmacokinetics of the Abraxane and Taxol paclitaxel formulations.
- Results of the study comparing Abraxane and Taxol that served as the basis for approval of Abraxane for advanced metastatic breast cancer.
- Abraxis BioScience initially proposed a 400 patient randomized safety study comparing Abraxane and Taxol in adjuvant treatment of node positive early breast cancer to be conducted prior to approval. The proposal has now changed to a post approval Phase 4 study of unspecified size.
- Study CA030, a single arm 30 patient study of dose dense Adriamycin plus Cytoxan every 2 weeks for 4 cycles followed by dose dense Abraxane 260 mg/m^2 every 2 weeks for 4 cycles for adjuvant treatment of node-positive early breast cancer.

Considerations on whether the Abraxis BioScience proposal is acceptable concern how similar or dissimilar the Abraxane and Taxol formulations are and the risk/benefit ratio of approving Abraxane for adjuvant node positive early breast cancer without an efficacy study of Abraxane in this setting. Taxol prolongs both disease-free survival and overall survival in this setting. The consequence of a decrement in efficacy in this setting would be very severe.

Pharmacokinetics of Abraxane compared to Taxol:

The pharmacokinetics of Abraxane and Taxol are different. The pharmacokinetics of Abraxane was compared to those of Taxol in 26 patients enrolled in a phase 1 study. Total paclitaxel concentrations (unbound plus bound) were assessed. Free, or unbound drug concentrations, which are believed to mediate drug activity, were not assessed. Abraxane was administered as a 260 mg/m^2 dosage, compared to 175 mg/m^2 of Taxol. The clearance of Abraxane-derived paclitaxel was 21.1 (± 44%) L/hr/m^2, compared to 14.8 (± 32%) L/hr/m^2 for Taxol. The volume of distribution of paclitaxel was 664 (± 48%) L/m^2 for Abraxane, compared to 433 (± 31%) L/m^2 for Taxol. The dose-adjusted Cmax and AUC were 88.7 (± 114%) ng/ml and 56.8 (± 46%) ng-hr/ml, respectively, for Abraxane, whereas, these parameters were 20.1 (± 56%) ng/ml and 71.9 (± 21%) ng-hr/ml, respectively, for Taxol. The elimination half-lives were 21.6 hours for Abraxane,

and 20.5 hours for Taxol. The pharmacokinetics of Abraxane was demonstrated to be linear from 80 to 375 mg/m^2. In contrast, Taxol demonstrates nonlinear pharmacokinetics from 135 to 175 mg/m^2, with greater than proportional increases in Cmax and AUC as dose increases. Over a five day period, paclitaxel and its two main inactive metabolites from Abraxane accounted for 25-26% (range 15 to 44%) of the administered drug that was recovered from urine and feces, whereas approximately 85% was recovered from the urine following Taxol administration. See Tables 1 and 2.

Table 1 Pharmacokinetics

Parameter (mean ± %CV)	**Abraxane* 260 mg/m^2 (n=14)**	**Taxol** 175 mg/m^2 (n=12)**	**Abraxane/Taxol Ratio**
C_{max} (ng/ml) ***	88.7 (114)	20.1 (56)	**4.4**
$AUC_{0-\infty}$ (ng-hr/ml) ***	56.8 (46)	71.9 (21)	**0.79**
CL (L/hr/m^2)	21.1 (44)	14.8 (32)	**1.43**
Vz (L/m^2)	664 (48)	433 (31)	**1.53**
$T^{1/2}$	21.6 hrs	20.5 hrs	

***Dose-normalized. *-30-minute infusion; **-3-hr infusion
AUC of Abraxane is less than that of Taxol
Not considered bioequivalent.

Table 2 Metabolism/Excretion

Compound	**% Dose (Abraxane*) 260 mg/m^2 (n=4-12)**		**% Dose (Taxol**) 225-250 mg/m^2 (n=5)**	
	Urine	**Feces**	**Urine**	**Feces**
Paclitaxel	3.92	2.77	NA	5
6α-hydroxypaclitaxel	0.15	18.0	NA	~66
3'-p-hydroxypaclitaxel	0.04	1.08	NA	NA
Total	4.11	21.89 (range 15-44)	14	71

Samples collected over 120 hr in both studies. *-30-minute infusion. **-3-hr infusion.
Results from Taxol Package Insert.

No comparative data are available in humans regarding tumor accumulation of either Abraxane or Taxol. Furthermore, free concentrations of drug are the likely mediators of paclitaxel activity, but no information is available for either drug. Only total paclitaxel (free plus bound) was measured. Therefore, it is unknown whether Abraxane or Taxol is more bioavailable.

Basis of approval for Abraxane for the metastatic breast cancer indication:

Study CA012-0 was a randomized, multi-center, open-label, phase 3 trial in 460 breast cancer patients. It was conducted at 70 sites located in Russia/Ukraine (77% of patients), United Kingdom (15%) and Canada and the U.S (9%). Patients were randomized to receive Abraxane (233 patients), 260 mg/m^2 as a 30-minute infusion, or 175 mg/m^2 paclitaxel injection (227 patients) as a 3-hour infusion. Fifty-nine percent of patients received study drug as second-line or greater than second-line therapy. Seventy-seven percent of the patients had previous exposure to anthracyclines.

The primary efficacy endpoint was response rate based on reconciled (investigators and independent radiology experts) assessment of target lesions through cycle 6. The observed response rates were Abraxane 21.5% and Taxol 11.1%, respectively and the estimated ratio of response rates (ABI-007/Taxol) was 1.899 with a 95% confidence interval (CI) of 1.228 – 2.937. These results suggest the superiority of ABI-007 with respect to the primary endpoint in the whole study population. See Table 3 below.

Table 3: Efficacy Results from Randomized Trial (from Abraxane Label)

		ABRAXANE 260 mg/m^2	Paclitaxel Injection 175 mg/m^2
Reconciled Target Lesion Response Rate (primary endpoint) [a]			
All randomized patients	Response Rate [95% CI]	50/233 (21.5%) [16.19% – 26.73%]	25/227 (11.1%) [6.94% – 15.09%]
	P-value [b]	0.003	
Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy[c]	Response Rate [95% CI]	20/129 (15.5%) [9.26% – 21.75%]	12/143 (8.4%) [3.85% – 12.94%]

[a] Reconciled Target Lesion Response Rate (TLRR) was the prospectively defined protocol specific endpoint, based on independent radiologic assessment of tumor responses reconciled with investigator responses (which also included clinical information) for the first 6 cycles of therapy. The reconciled TLRR was lower than the investigator Reported Response Rates, which are based on all cycles of therapy.

[b] From Cochran-Mantel-Haenszel test stratified by 1st line vs. > 1st line therapy.

[c] Prior therapy should have included an anthracycline unless clinically contraindicated

Time to progression (TTP) was a secondary endpoint. At the time of Abraxane approval, evaluation of this secondary endpoint was neither rigorous enough, nor mature enough to support a comparative efficacy claim in this single non-blinded trial. Thus, these results were not included in labeling. Updated TTP results were submitted to the FDA on July 21, 2006. The hazard ratio for TTP was 0.72, p=0.002 (log rank). However, the study was not blinded, the independent review of the radiologic findings was only conducted for the first six cycles of therapy and disease progression was not systematically assessed in all patients after completion of treatment. In addition, multiple analyses of TTP have been conducted using different criteria for progression and censoring without adjustments

of P-value. For these reasons, TTP results may not be sufficiently reliable to allow a labeling claim. This matter is currently under FDA review.

Overall survival was a secondary endpoint. Updated overall survival results were submitted to the FDA on July 21, 2006. As of the August 9, 2006 deadline for this briefing document, results from the submitted data have not been verified yet by the FDA. There was no difference in overall survival between the Abraxane and Taxol treatment groups. The hazard ratio (Abraxane/Taxol) was 0.90, p=0.348 (log rank). Survival was longer with Abraxane compared to Taxol in the subgroup of patients who failed combination therapy or relapsed within 6 months of adjuvant chemotherapy (p-value from the two-sided log rank test was 0.049). However, no conclusions can be drawn from a subgroup analysis when the main analysis was not statistically significant. P-values are not interpretable since there was no statistical analysis plan to analyze survival in this subgroup. In addition survival has been analyzed in multiple subgroups and the reported p values have not been adjusted for multiplicity. See Table 4 below.

Table 4 Patient Survival (From Sponsor's 19 July 2006 submission)

	ABI-007	Taxol	*P*-value[b]	Hazard Ratio
All Randomized Patients	N=233	N=227		
Patients Who died, n (%)	171(74%)	175(77%)		
Median Time to Death (weeks)	65.3	55.4	0.348	0.904
95% Confidence Interval	53.9, 77.0	48.3, 66.6		0.732, 1.116
Indication Population [a]	N=129	N=143		
Patients Who died, n (%)	98 (76%)	119 (83%)		
Median Time to Death (weeks)	57.0	46.9	0.049	0.764
95% Confidence Interval	45.6, 76.7	38.4, 55.4		0.584, 1.000

Note: Analysis included patient survival information during study-follow-up. Patients who did not die were censored at the last known time the patient was alive.

[a] Patients who failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy. Prior therapy included an anthracycline unless clinically contraindicated.

[b] P-value from log-rank test

Results from the survival data submitted in June 2005 showed that in the subgroup analysis of patients who received Abraxane or Taxol as 1st line treatment the trend is in favor of the Taxol patients (HR 1.2, 95% CI 0.86-1.71), while in the subgroup with second or greater line therapy the trend is in the opposite direction. This shows the hazard of doing subgroup analysis. See Table 5.

Table 5 Patient Survival (From Sponsor's Submission June 2005)

	ABI-007	Taxol	*P*-value	Hazard Ratio
ITT Population				
Patients Evaluated for Survival During Study	N=229	N=225		
Patients Who died, n (%)	172(75%)	175(78%)		
Median Time to Death (weeks)	65.0	55.3	0.322	0.899
95% Confidence Interval	53.4, 76.9	48.0, 66.4		0.728, 1.110
In First Line Therapy Patients Only				
Patients Evaluated for Survival During Study	N=98	N=89		
Patients Who died, n (%)	73 (74%)	60 (67%)		
Median Time to Death (weeks)	71.0	77.9	0.264	1.215
95% Confidence Interval	59.4, 87.7	58.1, 98.0		0.863, 1.709
In Patients Receiving Second or Greater Line Therapy				
Patients Evaluated for Survival During Study	N=131	N=136		
Patients Who died, n (%)	99 (76%)	115 (85%)	0.020	0.726
Median Time to Death (weeks)	56.4	46.7		
95% Confidence Interval	45.1, 76.9	39.0, 55.3		0.553, 0.952

Note: Analysis included patient survival information during study-follow-up.
Note: Patients who did not die were censored at the last known time the patient was alive.

Abraxane safety data from study CA012-0 showed that hypersensitivity reactions were fewer in the Abraxane arm compared with Taxol (4% vs. 12%). The incidence of Grade 4 neutropenia was lower for patients in the Abraxane arm compared to Taxol (9% vs. 22%) and the incidence of neutropenic fever was low and similar in both treatment arms (2% vs. 1%). The incidence of sensory neuropathy was greater in the Abraxane treatment arm (71% vs. 56% for all grades and 10% vs. 2% for grade 3). Gastrointestinal symptoms were more frequent with Abraxane compared to Taxol, nausea 30% versus 21%, vomiting 18% versus 9% and diarrhea 26% versus 15%. Serious adverse events (SAEs) were reported in 28% of Abraxane patients and 35% of Taxol patients, with neutropenia the most frequent SAE in both treatment groups. The most frequent toxicity leading to premature discontinuation was sensory neuropathy, Abraxane 3% and Taxol<1%. See Table 6.

Grade 3 sensory neuropathy was reported in 24 (10%) of Abraxane patients and 5 (2%) of Taxol patients. Abraxis claims that Abraxane patients with grade 3 neurosensory neuropathy improved to grade ≤ 2 faster than Taxol patients (Abraxane median time 22 days versus Taxol median time 79 days. The FDA does not agree with this claim. The

low incidence of grade 3 sensory neurotoxicity in the Taxol arm makes it difficult to compare the duration of neurotoxicity. There were only 5 Taxol patients with grade 3 sensory neuropathy. Also the endpoint is subjective and the study was not blinded.

Table 6: Frequency of Important Adverse Events in the Randomized Advanced Breast Cancer Study (Percent of Patients)

	Abraxane 260/30min (n=229)	Taxol 175/3h (n=225)
Bone Marrow		
Neutropenia		
< 2.0 x 10^9/L	**80**	**82**
< 0.5 x 10^9/L	**9**	**22**
Thrombocytopenia		
< 100 x 10^9/L	**2**	**3**
< 50 x 10^9/L	**<1**	**1**
Anemia		
< 11 g/L	**33**	**25**
< 8 g/L	**1**	**<1**
Infections	**24**	**20**
Febrile Neutropenia	**2**	**1**
Bleeding	**2**	**2**
Hypersensitivity Reaction		
All	**4**	**12**
Severe	**0**	**2**
Cardiovascular		
Vital Sign Changes		
Bradycardia	**<1**	**<1**
Hypotension	**5**	**5**
Severe Cardiovascular Events	**3**	**4**

	Abraxane 260/30min (n=229)	Taxol 175/3h (n=225)
Abnormal ECG		
All patients	**60**	**52**
Patients with Normal Baseline	**35**	**30**
Respiratory		
Cough	**6**	**6**
Dyspnea	**12**	**9**
Sensory Neuropathy		
Any Symptoms	**71**	**56**
Severe Symptoms	**10**	**2**
Myalgia / Arthralgia		
Any Symptoms	**44**	**49**
Severe Symptoms	**8**	**4**
Asthenia		
Any Symptoms	**47**	**38**
Severe Symptoms	**8**	**3**
Fluid Retention		
Any Symptoms	**10**	**8**
Severe Symptoms	**0**	**1**
Gastrointestinal		
Nausea		
Any Symptoms	**30**	**21**
Severe Symptoms	**3**	**<1**
Vomiting		
Any Symptoms	**18**	**9**
Severe Symptoms	**4**	**1**
Diarrhea		
Any Symptoms	**26**	**15**
Severe Symptoms	**<1**	**1**
Mucositis		
Any Symptoms	**7**	**7**
Severe Symptoms	**<1**	**0**
Alopecia	**90**	**94**
Hepatic **(**Patients with Normal Baseline)		
Bilirubin Elevations	**7**	**7**
Alkaline Phosphatase Elevations	**36**	**31**
AST (SGOT) Elevations	**39**	**32**
Injection Site Reaction	**1**	**1**

a. Taxol patients were premedicated. .

b. Severe events are NCI CTC ≥ grade 3 toxicity

Taxol approval in adjuvant breast cancer:

A Phase 3 intergroup study (Cancer and Leukemia Group B [CALGB], Eastern Cooperative Oncology Group [ECOG], North Central Cancer Treatment Group [NCCTG], and Southwest Oncology Group [SWOG]) randomized 3170 patients with node-positive breast carcinoma to adjuvant therapy with Taxol or to no further chemotherapy following four courses of doxorubicin and cyclophosphamide (AC). This multicenter trial was conducted in women with histologically positive lymph nodes following either a mastectomy or segmental mastectomy and nodal dissections. The study was designed to assess the efficacy and safety of three different dose levels of doxorubicin (A) and to evaluate the effect of the addition of Taxol administered following the completion of AC therapy. After stratification for the number of positive lymph nodes (1-3, 4-9, or 10+), patients were randomized to receive cyclophosphamide at a dose of 600 mg/m^2 and doxorubicin at doses of either 60 mg/m^2 (on day 1), 75 mg/m^2 (in two divided doses on days 1 and 2), or 90 mg/m^2 (in two divided doses on days 1 and 2 with prophylactic G-CSF support and ciprofloxacin) every 3 weeks for four courses and either Taxol 175 mg/m^2 as a 3-hour infusion every 3 weeks for four additional courses or no additional chemotherapy. Patients whose tumors were hormone receptor positive were to receive subsequent tamoxifen treatment (20 mg daily for 5 years); patients who received segmental mastectomies prior to study were to receive breast irradiation after recovery from treatment-related toxicities.

At the time of Taxol approval, median follow-up was 30.1 months. The primary analyses of disease-free survival and overall survival used multivariate Cox models, which included Taxol administration, doxorubicin dose, number of positive lymph nodes, tumor size, menopausal status, and estrogen receptor status as factors. Based on the model for disease-free survival, patients receiving AC followed by Taxol had a 22% reduction in the risk of disease recurrence compared to patients randomized to AC alone (HR = 0.78, 95% CI 0.67-0.91, p=0.0022). They also had a 26% reduction in the risk of death (HR = 0.74, 95% CI 0.60-0.92, p=0.0065). In summary, there was an overall favorable effect on disease-free and overall survival in the total population of patients with receptor-positive and receptor-negative tumors.

Most of the benefit was in the subgroup of patients with hormone receptor negative tumors. In patients with hormone receptor negative tumors, disease free survival HR= 0.68, 95% C.I. 0.55-0.85 and overall survival HR= 0.71, 95% C.I. 0.54-0.93. In patients with hormone receptor positive tumors, disease free survival HR = 0.92, 95% C.I. 0.73-1.16 and overall survival HR=0.83, 95% C.I. 0.59-1.18.

Table 7 Taxol Adjuvant Breast Cancer Intergroup Study: DFS and OS subset analyses (From Taxol Label)

Subset Analyses	ADJUVANT BREAST CANCER STUDY				
	Disease Free Survival			Overall Survival	
Patient Subset	No. of Patients	No. of recurrences	Hazard Ratio (95% CI)	No. of Deaths	Hazard Ratio (95% CI)
No. of Positive Nodes					
1-3	1449	221	0.72 (0.55-0.94)	107	0.76 (0.52-1.12)
4-9	1310	274	0.78 (0.61-0.99)	148	0.66 (0.47-0.91)
10+	360	129	9.93 (0.66-1.31)	87	0.90 (0.56-1.36)
Tumor Size (cm)					
≤ 2	1096	153	0.79 (0.57-1.08)	67	0.73 (0.45-1.18)
> 2and ≤ 5	1611	368	0.79 (0.64-0.97)	201	0.74 (0.56-0.98)
> 5	397	111	0.75 (0.51-1.08)	72	0.73 (0.46-1.16)
Menopausal Status					
Pre	1929	374	0.83 (0.67-1.01)	187	0.72 (0.54-0.97)
Post	1183	250	0.73 (0.57-0.93)	155	0.77 (0.56-1.06)
Receptor Status					
Positive [a]	2066	293	0.92 (0.73-1.16)	67	0.83 (0.59-1.18)
Negative/Unknown [b]	1055	331	0.68 (0.55-0.85)	216	0.71 (0.54-0.93)

[a] Positive for either estrogen or progesterone receptors
[b] Negative or missing for both estrogen and progesterone receptors (both missing=15)

Published updated data from the intergroup study, at a median follow-up of 69 months showed a 5 year relapse free survival of 65% in patients receiving AC compared to 70% of patients treated with AC plus Taxol (HR = 0.83, 95% CI 0.73-0.94, unadjusted p=0.0013). Survival at 5 years was 77% in the AC treatment group compared to 80% in the AC plus Taxol treatment arm (HR = 0.82, 95% CI 0.71-0.95, p=0.0061).

DISCUSSION

The main issue is whether Abraxane should be approved for the adjuvant treatment of node positive early breast cancer without a randomized trial demonstrating efficacy, based primarily on the results of the randomized study that served as the basis for Taxol approval for this indication.

Some of the considerations are:

- Paclitaxel is the active ingredient in both Taxol and Abraxane
- The Abraxane and Taxol formulations are very different, have different pharmacokinetics and are not bioequivalent using the tested regimens.
- Abraxane does not contain Cremophor. It is given by 30 minute infusion without premedication, while Taxol is given by 3 hour infusion and requires premedication. Abraxane does not require the specialized I.V. tubing required for Cremophor containing products.
- In the comparative trial in advanced breast cancer Taxol had a higher incidence of neutropenia and hypersensitivity reactions while Abraxane had a higher incidence of peripheral neuropathy, nausea, vomiting, diarrhea and asthenia.
- The primary endpoint of the metastatic disease study was tumor response rate. Abraxane had a higher tumor response rate. The sample size for this study was solely based on demonstrating tumor response effect. There was no type I error rate allocated for TTP or OS analysis. The sponsor has reported that there is no significant effect with respect to OS in the ITT population. Therefore, even if we allocate post-hoc a type I error rate (alpha) of 0.05 for the OS analysis, there is no alpha left for testing any subgroup analysis such as the Taxol indicated population, when the study has failed to demonstrate an effect in the overall population. Furthermore, the sponsor has conducted multiple analyses in multiple subgroups and not adjusted for multiplicity. Therefore, the p-values presented for the TTP or OS analyses are not interpretable.
- A non-inferiority trial comparing the disease-free survival of Abraxane and Taxol for adjuvant treatment of node positive early breast cancer may be large, if the treatments are indeed equal. However, if there is a strong trend favoring Abraxane (but not statistically significant at the 5% level), the trial size could be much smaller. A superiority trial could be even smaller with the trial size depending on the effect size that Abraxane is postulated to have.
- Taxol has been shown to increase both disease-free survival and overall survival in the adjuvant treatment of women with node positive early breast cancer. There is 22% reduction in the risk of disease recurrence compared to patients randomized to AC alone (HR = 0.78, 95% CI 0.67-0.91, p=0.0022). There is also a 26% reduction in the risk of death (HR = 0.74, 95% CI 0.60-0.92, p=0.0065). Any decrement in this efficacy would have severe consequences.