AETNA BETTER HEALTH®
Clinical Policy Bulletin:
Paclitaxel, Albumin-Bound (Abraxane)

Number: 0834

Policy

Aetna considers albumin-bound paclitaxel (Abraxane) medically necessary for the following indications:

Breast cancer (recurrent or metastatic) that is

- Hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative with visceral crisis; or
- HER2-negative and either hormone receptor-negative or hormone receptor-positive and endocrine therapy refractory; or
- Progressive with no clinical benefit after 3 consecutive endocrine therapy regimens or with symptomatic visceral disease

Epithelial ovarian cancer (persistent disease or recurrence)
Fallopian tube cancer (persistent disease or recurrence)
Melanoma (recurrent or metastatic)

- Incompletely resected or unresectable nodal recurrence; or
- Local/satellite and/or in-transit unresectable recurrence; or
- Recurrent or metastatic disease in persons with good performance status; or
- Unresectable stage III in-transit metastases

Non-small-cell lung cancer
Pancreatic cancer (in combination with gemcitabine for individuals with locally advanced unresectable/borderline resectable disease, or metastatic disease and good performance status)
Primary peritoneal cancer (persistent disease or recurrence)
Aetna considers albumin-bound paclitaxel experimental and investigational for the following criteria:

- Use not approved by the FDA; AND
- The use is unapproved and not supported by the literature or evidence as an accepted off-label use.

**Background**

Taxanes are conventional treatment for metastatic breast cancer (MBC); however, the solvents (e.g., ethanol and polyoxyethylated castor oil) employed as vehicles in these formulations result in severe toxicities. The Food and Drug Administration (FDA) approved a solvent-free formulation of paclitaxel for the treatment of MBC that uses 130-nanometer albumin-bound (nab) technology (Abraxane; nab-paclitaxel) to circumvent the requirement for solvents. Nab-paclitaxel utilizes the natural properties of albumin to reversibly bind paclitaxel, transport it across the endothelial cell, and concentrate it to the areas of the tumor. The proposed mechanism of drug delivery entails glycoprotein 60-mediated endothelial cell transcytosis of paclitaxel-bound albumin as well as accumulation in the areas of the tumor by albumin binding to SPARC (secreted protein, acidic and rich in cysteine; an albumin-binding matrix-associated protein). Published reports have shown that nab-paclitaxel is markedly more effective than paclitaxel formulated as cremophor EL (CrEL, Taxol), with almost double the response rate (RR), increased time to disease progression and increased overall survival (OS) in second-line patients. The absence of CrEL from the formulation is associated with decreased neutropenia and rapid improvement of peripheral neuropathy with nab-paclitaxel, compared with CrEL-paclitaxel. For these reasons, nab-paclitaxel can be infused using higher doses of paclitaxel than that achievable with CrEL-paclitaxel, with shorter infusion duration and without the requirement for corticosteroid and anti-histamine pre-medication to reduce the risk of solvent-mediated hypersensitivity reactions (Gradishar, 2006). In January 2005, the FDA approved albumin-bound paclitaxel (Abraxane) 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.

Yamamoto et al (2011) stated that nab-paclitaxel displays greater anti-tumor activity and less toxicity than solvent-base paclitaxel. In a phase I trial of nab-paclitaxel (single agent activity), the maximum tolerated dose (MTD) was 300 mg/m² with the dose limiting toxicities (DLT) being sensory neuropathy, stomatitis, and superficial keratopathy. In the metastatic setting, a pivotal comparative randomized phase III study demonstrated that nab-paclitaxel (at 260 mg/m² over a 30-min infusion without pre-medication every 3 weeks) mediated a superior objective response rate (ORR) and prolonged time to progression compared with solvent-based paclitaxel (at 175 mg/m² over a 3-hr injection with standard pre-medication). The nab-paclitaxel-treated group showed a higher incidence of sensory neuropathy than the solvent-based paclitaxel group. However, these adverse side effects rapidly resolved after interruption of treatment and dose reduction. Weekly administration of nab-paclitaxel was also more active and displayed less toxicity compared with 100 mg/m² docetaxel given tri-weekly. The authors noted that nab-paclitaxel has already been approved in 42 countries for the treatment of MBC previously treated with anthracycline, based on confirmation of the efficacy and manageable toxicity in the metastatic setting.

In a phase II clinical trial, Teneriello et al (2009) reported the effectiveness and toxicity of nab-paclitaxel in patients with recurrent ovarian, peritoneal, or fallopian tube cancer. A total of 47 patients enrolled in this study (44 assessable patients). Main inclusion criteria were histologically or cytologically confirmed epithelial cancer of the ovary, fallopian tube, or peritoneum (any stage, grade 2 to 3 if stage I) and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) or elevated cancer antigen 125 (CA-125) (greater than 70 U/ml) in patients without measurable disease. Patients received nab-paclitaxel 260 mg/m² administered intravenously (i.v.) for 30 mins on day 1 of a 21-day cycle for 6 cycles or until disease progression. Median age was 65.5 years; 76 % of patients had stage IIIC or IV disease, 81 % had Eastern Cooperative Oncology Group performance status of 0, and 94 % had prior surgery. For assessable patients, the ORR was 64 % (15 complete responses [CR] and 13 partial responses [PR] among 44 assessable patients). In patients evaluated with RECIST only, the ORR was 45 % (1 CR and 4 PR of 11 patients). In patients with only elevated CA-125, ORR was 82 % (7 CR and 2 PR of 11 patients). In patients meeting both RECIST and CA-125 criteria, the ORR was 64 % (7 CR and 7 PR of 22 patients). Median time to response was 1.3 months (range of 0.5 to 4.8 months). Estimated median progression-free survival (PFS) was 8.5 months. The most frequent grade 3 to 4 treatment-related toxicities were neutropenia (24 %) and neuropathy (9 %). The authors concluded that nab-paclitaxel is active in this group of patients with recurrent ovarian, peritoneal, or fallopian tube cancer. The ORR was 64 %; toxicities were manageable. They stated that further studies of nab-paclitaxel in combination with platinum are warranted.

In a phase II clinical study, Coleman et al (2011) evaluated the effects of nab-paclitaxel in the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer. Eligible patients had platinum- and taxane-resistant ovarian cancer, defined by persistent or progressive disease
following primary chemotherapy (n = 5) or recurrence within 6 months of treatment completion (n = 42). All patients had measurable disease, no prior therapy for recurrent disease and Gynecologic Oncology Group performance status of less than or equal to 2. Treatment was nab-paclitaxel, 100 mg/m² days 1, 8, and 15 on a 28-day schedule. The primary endpoint was RECIST version 1.0 RR, evaluated in a 2-stage design (with power of 0.90 for a RR of 25 % and with alpha of 0.05 for RR of 10 %). A total of 51 patients were enrolled of which 47 were evaluable; median time from front-line therapy completion to registration was 21 days. Patient demographics included median age of 59 (34 to 78) years, serous histology: 72 %, and high-grade: 81 %. Efficacy: 1 CR and 10 PR were confirmed (23 %); 17 patients (36 %) had stable disease (SD). The median PFS was 4.5 months (95 % confidence interval [CI]: 2.2 to 6.7); OS was 17.4 months (95 % CI: 13.2 to 20.8). Seventeen patients (36 %) had PFS greater than 6 months. Toxicity: there were no grade 4 events; grade 3 events were neutropenia (n = 6), anemia (n = 3), gastro-intestinal (n = 2), metabolic (n = 2), pain (n = 2), and leukopenia (n = 1). The authors concluded that nab-paclitaxel has note-worthy single-agent activity and is tolerable in this cohort of refractory ovarian cancer patients previously treated with paclitaxel.

In a phase III clinical trial, Socinski et al (2012) compared the safety and effectiveness of nab-paclitaxel plus carboplatin with solvent-based paclitaxel (sb-paclitaxel) plus carboplatin in advanced non-small-cell lung cancer (NSCLC). A total of 1,052 untreated patients with stage IIIb to IV NSCLC were randomly assigned 1:1 to receive 100 mg/m² nab-paclitaxel weekly and carboplatin at AUC 6 once every 3 weeks (nab-PC) or 200 mg/m² sb-paclitaxel plus carboplatin AUC 6 once every 3 weeks (sb-PC). The primary end point was objective ORR. On the basis of independent assessment, nab-PC demonstrated a significantly higher ORR than sb-PC (33 % versus 25 %; RR ratio, 1.313; 95 % CI: 1.082 to 1.593; p = 0.005) and in patients with squamous histology (41 % versus 24 %; RR ratio, 1.680; 95 % CI: 1.271 to 2.221; p < 0.001). Nab-PC was as effective as sb-PC in patients with non-squamous histology (ORR, 26 % versus 25 %; p = 0.808). There was an approximately 10 % improvement in PFS (median, 6.3 versus 5.8 months; hazard ratio [HR], 0.902; 95 % CI: 0.767 to 1.060; p = 0.214) and OS (median, 12.1 versus 11.2 months; HR, 0.922; 95 % CI: 0.797 to 1.066; p = 0.271) in the nab-PC arm versus the sb-PC arm, respectively. Patients greater than or equal to 70-year old and those enrolled in North America showed a significantly increased OS with nab-PC versus sb-PC. Significantly less grade greater than or equal to 3 neuropathy, neutropenia, arthralgia, and myalgia occurred in the nab-PC arm, and less thrombocytopenia and anemia occurred in the sb-PC arm. The authors concluded that administration of nab-PC as first-line therapy in patients with advanced NSCLC was effective and resulted in a significantly improved ORR versus sb-PC, achieving the primary end point; nab-PC produced less neuropathy than sb-PC.

The National Comprehensive Cancer Network’s Drugs and Biologics Compendium lists the following indications for albumin-bound paclitaxel (NCCN, 2013):

Breast cancer (recurrent or metastatic) that is

Hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative with visceral crisis; or
HER2-negative and either hormone receptor-negative or hormone receptor-positive and endocrine therapy refractory; or Progressive with no clinical benefit after 3 consecutive endocrine therapy regimens or with symptomatic visceral disease

Epithelial ovarian cancer (persistent disease or recurrence)
Fallopian tube cancer (persistent disease or recurrence)
Non-small cell lung cancer (first-line therapy for recurrence or metastasis in combination with carboplatin in performance status (PS) 0-2 patients)
Non-small cell lung cancer (for individuals who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite pre-medication, or for individuals in whom standard hypersensitivity pre-medications are contraindicated)
Pancreatic cancer (in combination with gemcitabine for individuals with locally advanced unresectable or metastatic disease and good performance status)
Primary peritoneal cancer (persistent disease or recurrence)

Albumin-bound paclitaxel is also being studied in other types of cancers such as adrenocortical cancer, angiosarcoma, bladder cancer, cervical cancer, endometrial cancer, head and neck cancer (including squamous-cell carcinoma of the hypopharynx, oropharynx, and oral cavity), hepatocellular cancer, melanoma, and prostate cancer. However the effectiveness of albumin-bound paclitaxel in these cancers has not been established.

Damascelli et al (2007) studied the safety and effectiveness of intra-arterial induction chemotherapy with nab-paclitaxel in advanced head and neck cancer. A total of 60 previously untreated patients with locally advanced squamous-cell carcinoma (SCC) of the oral cavity, oropharynx, or hypopharynx in stage T3/T4 and any nodal stage received 2 to 4 cycles of nab-paclitaxel by infusion into the external carotid artery or one of its branches, without pre-medication, at an initial dose of 230 mg/m2 and subsequently a reduced dose of 150 mg/m2. Response was evaluated by physical examination and multi-detector computed tomography in all patients, and also by positron emission tomography with [18F] fluorodeoxyglucose in 38 patients. Definitive treatment was surgery, chemotherapy, radiation therapy, or chemo-radiation therapy. Intra-arterial chemotherapy had a low incidence of complications and produced CR or PR in 45 of 60 treated patients (75 %). Seven patients (11.67 %) had SD and 8 (13.33%) had progressive disease (PD). High-grade bone marrow depression was rare. An unexpected toxicity was reversible facial nerve palsy on the side of infusion, which occurred in 6 patients at initial dosage. Reduction of the dose eliminated this specific toxicity without any loss of efficacy. The authors concluded that the promising response rates and tolerability of intra-arterial chemotherapy with nab-paclitaxel justify further investigation of this formulation, alone or in combination with other agents, in advanced SCC of the head and neck.

Desai et al (2009) noted that SPARC up-regulation is a poor prognostic factor in head and neck cancer. It was hypothesized that because of a SPARC-albumin interaction, tumoral SPARC facilitates the accumulation of albumin in the tumor and increases the effectiveness of nab-paclitaxel. These researchers tested this hypothesis by correlating the response to nab-paclitaxel and SPARC tumor
expression in a retrospective analysis of a 60-patient clinical study of nab-paclitaxel as monotherapy against head and neck cancer. A total of 16 tumor specimens were available for analysis. There were 11 responders (CR/PR) and 5 non-responders (SD/PD) among the 16 nab-paclitaxel-treated patients (12/16 SPARC-positive, 75 %). Response to nab-paclitaxel was higher for SPARC-positive patients (10/12, 83 %) than SPARC-negative patients (1/4, 25 %). The SPARC-negative patients exhibited significantly lower response than the ORR among all 60 patients (1/4, 25 % versus 45/60, 75 %). The authors concluded that although preliminary, data are supportive of the hypothesis that SPARC over-expression may correlate with response to nab-paclitaxel. They stated that if confirmed in larger studies, treatment with nab-paclitaxel may convert a poor prognosis SPARC-positive patient population into a group with better clinical outcomes.

Fader and Rose (2009) examined the effects of Abraxane for the treatment of gynecologic cancer patients with severe hypersensitivity reactions to paclitaxel. A total of 5 patients with gynecologic cancers (cervical cancer, n = 1; endometrial cancer, n = 2; and ovarian cancer, n = 2) received Abraxane after having a hypersensitivity reaction to paclitaxel. All 5 patients tolerated Abraxane well, experiencing no reactions or major side effects to the drug. The authors concluded that Abraxane is well-tolerated in women with gynecologic cancer who have experienced a paclitaxel-associated hypersensitivity reaction. They stated that further studies are ongoing to determine the clinical activity of Abraxane in the treatment of these malignancies.

In a phase II clinical trial, Shepard et al (2009) examined the safety and effectiveness of neoadjuvant nab-paclitaxel in patients with high-risk, locally advanced prostate cancer. Eligible patients had locally advanced prostatic adenocarcinoma, clinical stage cT2b or greater, Gleason score 8 or greater, or serum prostate specific antigen (PSA) 15 ng/ml or greater without metastatic disease. Patients received 2 cycles of 150 mg/m2 nab-paclitaxel weekly for 3 weeks during each 4-week cycle, followed by radical prostatectomy with bilateral lymphadenectomy. Efficacy assessments included pathological and PSA response. A total of 19 patients completed neoadjuvant therapy and 18 underwent radical prostatectomy. Median pre-treatment PSA was 8.5 ng/ml and median Gleason score was 8. Despite the lack of complete pathological responses 5 of 18 patients (28 %) had organ-confined disease and 9 of 18 (50 %) had specimen-confined disease. Post-chemotherapy PSA was decreased in 18 of 19 (95 %) patients and median decrease was 2.9 ng/ml (35 %, p < 0.001). An initial PSA after radical prostatectomy of 0.02 ng/ml or less was achieved in 17 of 18 (94 %) patients. There were no significant peri-operative complications. Cytoplasmic vacuolization (focal in 10 and extensive in 7) was evident in all but 1 patient (94 %); 10 patients (56 %) had grade-3 and 1 had grade-4 neutropenia with no febrile neutropenia. The authors concluded that neoadjuvant nab-paclitaxel was well-tolerated. Similar to their experience with neoadjuvant docetaxel, there were no pathological CR although a possible histological anti-tumor effect was observed.

Hirata and colleagues (2011) evaluated the effectiveness of taxane regimens in patients with metastatic angiosarcoma. A total of 41 patients with metastatic angiosarcoma treated at the National Cancer Center Hospital between January 1982 and January 2009 were retrospectively classified into 3 groups according to
the treatment type: (i) taxane (n = 11), (ii) non-taxane (n = 14), and (iii) best supportive care (BSC; n = 16). The taxane group received paclitaxel (n = 6), docetaxel (n = 4), or nab-paclitaxel (n = 1), and the non-taxane group received mainly doxorubicin-containing regimens (n = 12). The differences in PFS among the 3 groups were statistically significant (p < 0.001). After adjusting for prognostic factors, the taxane group had significantly longer PFS than the non-taxane (HR: 0.282; 95 % CI: 0.086 to 0.923; p = 0.036) and BSC (HR: 0.015; 95 % CI: 0.003 to 0.083; p < 0.001) groups. Overall survival was also significantly longer in the taxane group than in the other groups. The authors concluded that a taxane regimen may be more effective than a non-taxane regimen for treating patients with metastatic angiosarcoma.

In a phase I study, McKiernan et al (2011) evaluated the DLT and maximum deliverable dose of intra-vesical nab-paclitaxel in patients with non-muscle invasive bladder cancer. Inclusion criteria for trial were recurrent high-grade Ta, T1 and Tis transitional cell carcinoma of the bladder for which at least 1 prior standard intra-vesical regimen failed. Six weekly instillations of nab-paclitaxel were administered with a modified Fibonacci dose escalation model used until the maximum deliverable dose was achieved. The primary end point was DLT and the secondary end point was RR. A total of 18 patients were enrolled in the study. One patient demonstrated measurable systemic absorption after 1 infusion. Grade 1 local toxicities were experienced by 10 (56 %) patients with dysuria being the most common, and no grade 2, 3 or 4 drug-related local toxicities were encountered. Of the 18 patients, 5 (28 %) had no evidence of disease at post-treatment evaluation. The authors concluded that intra-vesical nab-paclitaxel exhibited minimal toxicity and systemic absorption in the first human intra-vesical phase I trial. They stated that a larger phase II study has begun to formally evaluate the activity of this regimen.

In a phase II clinical trial, Hersh et al (2010) evaluated the safety and effectiveness of nab-paclitaxel in previously treated (PT) and chemotherapy-naive (CN) patients with metastatic melanoma (MM). Patients with histologically or cytologically confirmed, measurable MM were enrolled. Nab-paclitaxel was administered intravenously weekly for 3 of 4 weeks at a dose of 100 mg/m2 (in PT patients) or 150 mg/m2 (in CN patients). A total of 37 patients were treated in each cohort. The RR was 2.7 % in the PT cohort and 21.6 % in the CN cohort; the response plus SD rate was 37.8 % and 48.6 % in the PT and CN cohorts, respectively. The median PFS was 3.5 months and 4.5 months, and the median OS was 12.1 months and 9.6 months, respectively. The probability of being alive and free of disease progression at 6 months was 27 % for the PT cohort and 34 % for the CN cohort; the probability of surviving 1 year was 49 % and 41 %, respectively, for the PT and CN cohorts. Approximately 78 % of the PT patients and 49 % of the CN patients were treated without dose reduction. Eight (22 %) CN patients discontinued therapy because of toxicities. Drug-related toxicities included grade 3 to 4 (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 3.0]) neuropathy, alopecia, neutropenia, and fatigue. The authors concluded that nab-paclitaxel was found to be well-tolerated and demonstrated activity in both PT and CN patients with MM. The RR, PFS, and OS compared favorably with current standard dacarbazine therapy and combination therapies for melanoma. They stated that nab-paclitaxel therapy of MM should be investigated further in controlled clinical trials.
Kottschade et al (2011) noted that there is increasing evidence that paclitaxel and carboplatin are clinically active in the treatment of MM. ABI-007 is an albumin-bound formulation of paclitaxel that has demonstrated single-agent activity against MM. In a parallel phase II trial, these researchers examined the effects of nab-paclitaxel in patients with unresectable stage IV melanoma who were either CN or PT. The treatment regimen consisted of ABI-007 (100 mg/m2) and carboplatin AUC administered on days 1, 8, and 15 every 28 days. The primary aim of this study was ORR (RECIST). A total of 76 patients (41 CN and 35 PT) were enrolled between November 2006 and July 2007. Three patients withdrew consent prior to starting treatment. The median number of treatment cycles was 4. There were 10 (25.6 %) responses (1 CR and 9 PR) in the CN cohort (90 % CI: 16.7 % to 42.3 %) and 3 (8.8 %) responses (3 PR) in the PT cohort (90 % CI: 2.5 % to 21.3 %). Median PFS was 4.5 months in the CN cohort and 4.1 months in the PT cohort. Median OS was 11.1 months in the CN group and 10.9 months in the PT group. Severe toxicities in both groups (Common Terminology Criteria for Adverse Effects version 3.0 greater than or equal to grade 3) included neutropenia, thrombocytopenia, neurosensory problems, fatigue, nausea, and vomiting. The authors concluded that the weekly combination of ABI-007 and carboplatin appears to be moderately well-tolerated, with promising clinical activity as therapy in patients who are chemotherapy naive and with modest anti-tumor activity in those previously treated.

Fu and associates (2011) stated that liver involvement in patients with metastatic cancer has limited options and poor outcomes. In a phase I clinical trial, these researchers examined the safety, activity, and pharmacokinetic characteristics of hepatic arterial infusion (HAI) of nab-paclitaxel. Cohorts of 3 patients having predominant hepatic metastases received HAI nab-paclitaxel at 3 dose levels (180, 220, and 260 mg/m2, respectively) infused for more than 1 hr every 3 weeks (3 + 3 design). Some patients participated in comparative pharmacokinetic studies (i.v. versus HAI), receiving their first course i.v., to determine peak concentrations and effect of first-pass hepatic extraction compared with subsequent courses administered by HAI. The highest dose level was expanded to determine the safety and activity of HAI nab-paclitaxel. A total of 38 patients were treated. There were no DLT at doses up to 260 mg/m2. Common adverse events included alopecia, fatigue, myelosuppression, nausea, and vomiting. Three patients had SD for 4 or more months and 2 patients (1 of 12 with breast cancer and 1 of 1 with cervical cancer) achieved a PR lasting for 5 and 15 months, respectively. Peak concentrations were lower (approximately 50 %) with greater hepatic extraction of drug (approximately 42 %) following HAI than i.v. infusion based on AUC comparison of drug exposure. The authors stated that HAI nab-paclitaxel showed partial hepatic extraction. At doses 260 mg/m2 or less given for 1 hr every 3 weeks, the treatment was well-tolerated and showed activity in advanced cancer patients with predominant liver metastases.

Demeure et al (2012) hypothesized that molecular technology including gene expression profiling could expose novel targets for therapy in adrenocortical carcinoma (ACC). SPARC is proposed to act as a mechanism for the increased efficacy of nab-paclitaxel. In this study, the transcriptomes of 19 ACC tumors and 4 normal adrenal glands were profiled on Affymetrix U133 Plus2 expression microarrays to identify genes representing potential therapeutic targets.
Immunohistochemical analysis for target proteins was performed on 10 ACC, 6 benign adenomas, and 1 normal adrenal gland. Agents known to inhibit selected targets were tested in comparison with mitotane in the 2 ACC cell lines (H295R and SW-13) as well as in mouse xenografts. SPARC expression is increased in ACC samples by 1.56 +/- 0.44 fold (μ +/- standard deviation). Paclitaxel and nab-paclitaxel showed in-vitro inhibition of H295R and SW-13 cells at IC50 concentrations of 0.33 μM and 0.0078 μM for paclitaxel and 0.35 μM and 0.0087 μM for nab-paclitaxel compared with mitotane concentrations of 15.9 μM and 46.4 μM, respectively. In-vivo nab-paclitaxel treatment showed a greater decrease in tumor weight in both xenograft models than mitotane. The authors concluded that biological insights garnered through expression profiling of ACC tumors merited further investigation into the use of nab-paclitaxel for the treatment of ACC.

A phase III trial (Socinski et al, 2012) compared the efficacy and safety of albumin-bound paclitaxel (nab-paclitaxel) plus carboplatin with solvent-based paclitaxel (sb-paclitaxel) plus carboplatin in advanced non-small-cell lung cancer (NSCLC). In all, 1,052 untreated patients with stage IIIB to IV NSCLC were randomly assigned 1:1 to receive 100 mg/m² nab-paclitaxel weekly and carboplatin at area under the concentration-time curve (AUC) 6 once every 3 weeks (nab-PC) or 200 mg/m² (2) sb-paclitaxel plus carboplatin AUC 6 once every 3 weeks (sb-PC). The primary end point was objective overall response rate (ORR). On the basis of independent assessment, nab-PC demonstrated a significantly higher ORR than sb-PC (33% v 25%; response rate ratio, 1.313; 95% CI, 1.082 to 1.593; P = .005) and in patients with squamous histology (41% v 24%; response rate ratio, 1.680; 95% CI, 1.271 to 2.221; P < .001). nab-PC was as effective as sb-PC in patients with nonsquamous histology (ORR, 26% v 25%; P = .808). There was an approximately 10% improvement in progression-free survival (median, 6.3 v 5.8 months; hazard ratio [HR], 0.902; 95% CI, 0.767 to 1.060; P = .214) and overall survival (OS; median, 12.1 v 11.2 months; HR, 0.922; 95% CI, 0.797 to 1.066; P = .271) in the nab-PC arm versus the sb-PC arm, respectively. Patients ≥ 70 years old and those enrolled in North America showed a significantly increased OS with nab-PC versus sb-PC. Significantly less grade ≥ 3 neuropathy, neutropenia, arthralgia, and myalgia occurred in the nab-PC arm, and less thrombocytopenia and anemia occurred in the sb-PC arm. The investigators concluded that the administration of nab-PC as first-line therapy in patients with advanced NSCLC was efficacious and resulted in a significantly improved ORR versus sb-PC, achieving the primary end point. nab-PC produced less neuropathy than sb-PC.

The 2013 NCCN Drugs & Biologics Compendium provided a 2A recommendation on the use of albumin-bound paclitaxel for the treatment of melanoma. It notes that albumin-bound paclitaxel can be used as a single agent for the treatment of melanoma in the following:

- Incompletely resected or unresectable nodal recurrence
- Local/satellite and/or in-transit unresectable recurrence
- Recurrent or metastatic disease in persons with good performance status
- Unresectable stage III in-transit metastases

Adkins et al (2013) stated that CR at the primary tumor site as assessed by clinical examination following induction chemotherapy with PF (cisplatin and 5-fluorouracil [5-FU]) is a favorable predictive factor for OS and disease control in patients with
locally advanced squamous cell carcinoma of the head and neck. In most series, the rate of CR at the primary site after induction PF was 20 % to 30 %. These researchers evaluated the effectiveness and feasibility of induction nanoparticle albumin-bound paclitaxel (Nab-PTX) and cetuximab given with PF (ACPF) followed by definitive chemo-radiation therapy (CRT) in a phase II trial. Patients with squamous cell carcinoma of the head and neck were treated with ACPF (Nab-PTX 100 mg/m(2)/week; cetuximab 250 mg/m(2)/week; cisplatin 75 mg/m(2) on day 1; 5-FU 750 mg/m(2)/day on days 1 through 3) every 21 days for 3 cycles followed by CRT (cisplatin 100 mg/m(2) on days 1, 22, and 43 of RT). Complete response at the primary tumor site after 2 cycles of ACPF was the primary endpoint. A total of 30 patients were enrolled, of which 22 (73 %) had large (T3/T4) primary tumors. The CR rate at the primary tumor site after 2 cycles of ACPF was 53 % and the overall response rate was 100 %. Twenty-nine (96 %) patients completed 3 cycles of ACPF, 26 (90 %) completed definitive RT per protocol, and 22 of the 27 evaluable patients (81 %) received greater than 2 of the 3 planned doses of cisplatin with RT. The estimated 2-year OS and PFS rates were 84 % and 65 %, respectively. The authors concluded that induction ACPF resulted in a high CR rate (53 %) at the primary tumor site even in large tumors and did not adversely affect delivery of definitive CRT. Moreover, they stated that further investigation of ACPF is warranted.

Kottschade et al (2013) conducted a phase 2 trial in chemotherapy-naive patients with unresectable stage IV MM who were randomized to temozolomide (200 mg/m(2) on days 1 through 5) and bevacizumab (10 mg/kg intravenously on days 1 and 15) every 28 days (Regimen TB) or Nab-PTX (100 mg/m(2), or 80 mg/m(2) post-addendum 5 secondary to toxicity, on days 1, 8, and 15), bevacizumab (10 mg/kg on days 1 and 15), and carboplatin (area under the curve [AUC] 6 on day 1, or AUC 5 post-addendum 5) every 28 days (Regimen ABC). Accrual goal was 41 patients per regimen. The primary aim of this study was to estimate PFS rate at 6 months (PFS6) in each regimen. A regimen would be considered promising if its PFS6 rate was greater than 60 %. A total of 93 eligible patients (42 TB and 51 ABC) were enrolled. The majority of patients had M1c disease (20 TB and 26 ABC). The median PFS and OS times with ABC were 6.7 months and 13.9 months, respectively. Median PFS time and median OS with TB were 3.8 months and 12.3 months, respectively. The most common severe toxicities (greater than or equal to grade 3) in both regimens were cytopenias, fatigue, and thrombosis. Among the first 41 patients enrolled onto each regimen, PFS6 rate was 32.8 % (95 % CI: 21.1 % to 51.2 %) for TB and 56.1 % (90 % CI: 44.7 % to 70.4 %) for ABC. The authors concluded that the addition of bevacizumab to Nab-PTX and carboplatin showed promising activity despite tolerability issues.

Shi and colleagues (2013) examined the safety and effectiveness of Nab-PTX combined with cisplatin (DDP) in patients with metastatic esophageal SCC (ESCC). Patients with histologically confirmed ESCC were treated with Nab-PTX 250 mg/m(2) and DDP 75 mg/m(2) intravenously on day 1, every 21 days. Evaluation was performed after every 2 cycles of therapy and the therapy was continued until disease progression or unacceptable toxicity. From April 2010 to December 2012, a total of 33 patients were enrolled – 10 patients had recurrent and metastatic tumors after surgery and 23 patients were diagnosed with unresectable metastatic disease. Patients received a median of 4 cycles of therapy (ranging from 2 to 6 cycles). Twenty patients achieved PR and 9 patients
achieved SD; no CR was observed. The objective response rate was 60.6 % and the disease control rate was 87.9 %. The median PFS was 6.2 months (95 % CI: 4.0 to 8.4 months) and the median OS was 15.5 months (95 % CI: 7.6 to 23.4 months). Only 4 patients experienced grade 3 adverse events, including vomiting, neutropenia, and sensory neuropathy. The most common adverse events were nausea/vomiting (81.8 %), neutropenia (63.6 %), leucopenia (48.5 %), anemia (24.2 %) and sensory neuropathy (24.2 %). The authors concluded that the combination of Nab-PTX and DDP is a highly effective and well-tolerated first-line treatment in metastatic ESCC. The findings of this study were confounded by the combinational use of albumin-bound paclitaxel and cisplatin. The clinical value of albumin-bound paclitaxel in the treatment of metastatic esophageal squamous cell carcinoma needs to be ascertained in well-designed studies.

Zhang et al (2013) noted that gastric cancer is the second common cause of cancer related death worldwide and lacks highly effective treatment for advanced disease. In this study, human gastric cancer cell lines AGS, NCI-N87 and SNU16 were studied. Nab-paclitaxel inhibited cell proliferation with an IC50 of 5 nM in SNU16, 23 nM in AGS and 49 nM in NCI-N87 cells after 72-hour treatment, which was lower than that of oxaliplatin (1.05 μM to 1.51 μM) and epirubicin (0.12 μM to 0.25 μM). Nab-paclitaxel treatment increased expression of the mitotic-spindle associated phospho-stathmin irrespective of the baseline total or phosphorylated stathmin level, and induced mitotic cell death as confirmed through increased expression of cleaved-PARP and caspase-3. After a 2-week nab-paclitaxel, oxaliplatin or epirubicin treatment, the average in-vivo local tumor growth inhibition rate was 77, 17.2 and 21.4 %, respectively (p=0.002). Effects of therapy on tumoral proliferative and apoptotic indices corresponded with tumor growth inhibition data, while expression of phospho-stathmin also increased in tissues. There was an increase in median animal survival after Nab-PTX treatment (93 days) compared to controls (31 days, p=0.0002), oxaliplatin (40 days, p=0.0007) or to docetaxel therapy (81 days, p=0.0416). The strong anti-tumor activity of Nab-PTX in experimental gastric cancer supports such microtubule-inhibitory strategy for clinical application. Nab-paclitaxel benefits were observed independent from phosphorylated stathmin expression at baseline, putting into question the consideration of Nab-PTX use in gastric cancer based on this putative biomarker.

In a phase II clinical trial, Ko and associates (2013) evaluated the effectiveness and tolerability of Nab-PTX in patients with platinum-refractory urothelial cancer. In this open-label, single-group, 2-stage study at 5 centers in Canada, these researchers enrolled patients aged at least 18 years with histologically confirmed, locally advanced, or metastatic measurable urothelial cancer, with documented progression on or within 12 months of treatment with 1 previous platinum-containing regimen. Patients received Nab-PTX at 260 mg/m(2) intravenously every 3 weeks. Treatment continued until disease progression or occurrence of unacceptable toxic effects. The primary end-point was objective tumor response, defined by a CR or PR according to Response Evaluation Criteria In Solid Tumors (version 1.0) criteria. Tumor response and safety were assessed in all patients who received at least 1 cycle of Nab-PTX. These investigators enrolled 48 patients between October 16, 2008, and June 23, 2010. Patients received a median of 6 cycles (range of 1 to 15). A total of 47 patients were evaluable; 1 (2.1 %) had a CR and 12 (25.5 %) had PRs, resulting in an overall response of 27.7 %
(95 % CI: 17.3 to 44.4). The most frequently recorded adverse events of any grade were fatigue (38 of 48; 79 %), pain (37 of 48; 77 %), alopecia (34 of 48; 71 %), and neuropathy (30 of 48; 77 %). The most frequently recorded adverse events of grade 3 or higher were pain (11 of 48; 23 %), fatigue (5 of 48; 23 %), hypertension (3 of 48; 6 %), neuropathy (3 of 48, 6 %), and joint stiffness or pain (2 of 48; 4 %). The authors concluded that Nab-PTX was well-tolerated in this population of patients with pre-treated advanced urothelial cancer with an encouraging tumor response. Moreover, they stated that these results warrant further study of Nab-PTX in second-line treatment of urothelial cancer.

UpToDate reviews on “Treatment of refractory and relapsed small cell lung cancer” (Kelly, 2013) and “Treatment protocols for small-cell carcinoma of the lung” (Brenner et al, 2013) do not mention the use of albumin-bound paclitaxel as a therapeutic option for small cell lung cancer. Furthermore, according to the 2013 NCCN Drugs & Biologics Compendium, small cell lung cancer is not a recommended indication of Abraxane (albumin-bound paclitaxel).

NCCN’s clinical practice guideline on “Occult Primary (Cancer of Unknown Primary (CUP)” (Version 3.2014) does not mention the use of albumin-bound paclitaxel as a therapeutic option. Also, NCCN’s Drugs & Biologics Compendium (2014) does not list cancer of unknown primary as a recommended indication of albumin-bound paclitaxel.

NCCN’s clinical practice guideline on “Anal cancer” (Version 1.2015) does not mention the use of albumin-bound paclitaxel as a therapeutic option. Also, NCCN’s Drugs & Biologics Compendium (2014) does not list cancer of unknown primary as a recommended indication of albumin-bound paclitaxel.

An UpToDate review on “Treatment of advanced, unresectable gallbladder cancer” (Mehrotra, 2014) does not mention the use of paclitaxel as a therapeutic option. Also, per NCCN Drugs & Biologics Compendium (2014), gallbladder cancer is not a recommended indication of paclitaxel (albumin bound).

Furthermore, there is currently no clinical trial investigating the use of paclitaxel (albumin bound) for the treatment of gallbladder cancer.


In a prospective, single-arm, single-center, pilot study, Han et al (2012) evaluated the effectiveness of weekly paclitaxel/carboplatin chemotherapy in patients with locally advanced, metastatic, or recurrent vulvar squamous cell carcinoma. This study was initiated to examine response rate of 9 weekly courses of paclitaxel (60 mg/m) and carboplatin (area under the curve, 2.7). These researchers used this regimen in the neoadjuvant or metastatic setting when surgery would cause serious morbidity or was not an option owing to distant metastases. Primary outcome was response rate, measured according to Response Criteria in Solid Tumors criteria. Treatment toxicity, surgical morbidity, and type of surgery were also evaluated. These investigators treated 6 patients in the period between May 2009 and May 2011, of which 4 patients had a diagnosis of locally advanced disease and 2 patients had a diagnosis of recurrent disease. A median number of 7.5 cycles of paclitaxel/carboplatin weekly was administered (range of 3 to 9). No objective response was observed. Paclitaxel/carboplatin weekly was discontinued after a mean of 4.3 weekly cycles in 3 patients owing to local disease progression.
After a median follow-up of 4.2 months (range of 1 to 29 months), 3 patients died as a result of progressive disease; and 1 patient died as a consequence of intercurrent disease. The 2 remaining patients underwent radical vulvectomy + bilateral inguino-femoral lymphadenectomy after neoadjuvant chemotherapy. The main chemotherapy-related toxicity was anemia and could be managed conservatively with erythropoietin and intravenous iron therapy. The authors concluded that weekly administration of paclitaxel-carboplatin has limited clinical benefit in the treatment of vulvar squamous cell carcinoma.

Raspagliesi et al (2014) evaluated the efficacy and toxicity of paclitaxel and cisplatin in locally advanced vulvar cancer. From 2002 to 2009, 10 patients with stage III-IV locally advanced squamous cell carcinoma of the vulva were prospectively treated with 3 courses of paclitaxel-ifosfamide-cisplatin or paclitaxel-cisplatin; 9 of them subsequently underwent radical local excision or radical partial vulvectomy and bilateral inguino-femoral lymphadenectomy. The clinical response rate of all enrolled patients was 80%, whereas the pathological responses included 1 case with complete remission, 2 with persistent carcinoma in-situ, and 6 invasive cancer cases with tumor shrinkage of more than 50%. Four patients had positive nodes; 40% of patients experienced grade 3 to 4 bone marrow toxicity, which was successfully managed with granulocyte-colony stimulating factor, even in cases of elderly patients. Median progression-free survival after surgery was 14 months (range of 5 to 44 months). Six of the 7 recurrent cases were local, and 3 of them were treated with salvage surgery while the other 3 received radiation with or without chemotherapy. After a median follow-up period of 40 months (range of 5 to 112 months), 55.5% of patients remained alive with no evidence of disease, including 2 long-term survivors after recurrence at 5 and 9 years. The authors concluded that based on the high response rate and manageable toxicity, multimodality treatments including concurrent chemoradiation or different regimens of neoadjuvant chemotherapy, with paclitaxel and cisplatin with or without ifosfamide followed by surgery could be considered as a therapeutic option for locally advanced vulvar cancer. (This was a small study and albumin-bound paclitaxel was not the drug used)

An UpToDate review on “Vulvar cancer: Staging, treatment, and prognosis” (Elkas et al, 2014) states that “Primary chemoradiotherapy or brachytherapy are therapeutic options that may allow sparing of rectal function or obviate the need for surgery entirely in women with primary carcinoma of the Bartholin gland. Chemoradiation may be particularly effective in cancers with squamous histology. For advanced disease, single case reports describe activity for liposomal doxorubicin and paclitaxel”. This review does not mention albumin-bound paclitaxel.

Furthermore, NCCN’s Drugs & Biologics Compendium (2014) does not list vulvar carcinoma as a recommended indication of albumin-bound paclitaxel.
HCPCS codes covered if selection criteria are met:

J9264 Injection, paclitaxel protein-bound particles, 1 mg

ICD-9 codes covered if selection criteria are met:

157.0 - 157.9 Malignant neoplasm of pancreas
158.0 - 158.9 Malignant neoplasm of peritoneum, unspecified
162.0 - 162.9 Malignant neoplasm of trachea, bronchus and lung [non-small-cell lung cancer]
172.0 - 172.9 Malignant melanoma of skin
174.0 - 175.9 Breast cancer
183.0 - 183.9 Malignant neoplasm of ovary and other uterine adnexa

ICD-9 codes not covered for indications listed in the CPB (not all inclusive):

142.0 Malignant neoplasm of parotid gland
150.0 - 150.9 Malignant neoplasm of esophagus[squamous-cell]
151.0 - 151.9 Malignant neoplasm of stomach
155.0 - 155.2 Malignant neoplasm of liver and intraheptic bile ducts
162.2 - 162.9 Malignant neoplasm of lung [small cell]
176.0 - 176.9 Kaposi’s sarcoma
180.0 - 180.9 Malignant neoplasm of cervix uteri
182.0 Malignant neoplasm of corpus uteri, except isthmus
185 Malignant neoplasm of prostate
188.0 - 188.9 Malignant neoplasm of bladder [urothelial]
194.0 Malignant neoplasm of adrenal gland
195.0 Malignant neoplasm of head, face and neck

The above policy is based on the following references:


