BlueCross BlueShield of Alabama

"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:
Abraxane® (paclitaxel, protein-bound)

Policy #:	650	Effective Date: February 26, 2018
Category:	Pharmacology	Last Review Date: February 2018

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Abraxane® (paclitaxel, protein bound), is a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilized microtubules by preventing depolymerization. The resulting stability inhibits the normal dynamic reorganization of the microtubule network that is necessary for interphase and mitotic cellular functions.

Policy:

Effective for dates of service on and after February 26, 2018:

Blue Advantage will treat **Abraxane (paclitaxel, protein-bound)** as a **covered benefit** for treatment of **recurrent/metastatic breast cancer** for the following indications:

- As a single agent for HER2 negative disease with visceral crisis and the agent is being used as first line therapy, **OR**
- In combination with trastuzumab (Herceptin)for HER2 positive disease with visceral crisis and being used as first line therapy, **OR**
- After failure of combination chemotherapy for metastatic disease, that contained an anthracycline or has documented intolerance to an anthracycline.

AND

- Has relapsed within 6 months of adjuvant therapy, OR
- Received prior therapy with paclitaxel in prior line of therapy, or has documented intolerance to paclitaxel or docetaxel.

Blue Advantage will treat **Abraxane (paclitaxel, protein-bound)** as a **covered benefit** for treatment of **locally advanced or metastatic non-small cell lung cancer** for the following indications:

- When used as a single agent, AND
- *ECOG performance status is 2

OR

- Used in combination with carboplatin or cisplatin, AND
- *ECOG performance status is 0-2, AND
- Patient is not a candidate for curative surgery or radiation therapy

And one of the following:

- When used as first line therapy, OR
- When used as subsequent therapy for ALK/EGFR/ROS1/BRAF positive tumors after targeted therapy, OR
- When used as subsequent therapy for PD-L1 expression-positive (≥50%) and ALK/EGFR/ROS1/BRAF negative tumors and prior pembrolizumab (Keytruda) therapy.

OR

- When substituted for either paclitaxel or docetaxel secondary to documented allergic reaction or when conventional pre-medications are contraindicated.

Blue Advantage will treat Abraxane (paclitaxel, protein-bound) as a **covered benefit** for treatment of **metastatic adenocarcinoma of the pancreas** when used as first line or subsequent therapy in combination with gemcitabine and *ECOG performance status in 0-1.

Blue Advantage will treat Abraxane (paclitaxel, protein-bound) as a **covered benefit** for treatment of **metastatic or unresectable melanoma** when used as a single agent as second line therapy for disease progression for individuals with *ECOG performance status of 0-2.

Blue Advantage will treat Abraxane (paclitaxel, protein-bound) as a **covered benefit** for treatment of **ovarian cancer (epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer**) when used as a single agent for persistent disease or recurrence.

Blue Advantage will treat Abraxane (paclitaxel, protein-bound) as a **non-covered benefit** and as **investigational** when the above criteria are not met and all other indications.

*ECOG – Eastern Cooperative Oncology Group

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Metastatic Breast Cancer

Breast cancer is managed by various treatment modalities including combinations of surgery, radiation therapy, chemotherapy, and hormone therapy. The prognosis and selection of therapies can be affected by clinical and pathologic features of the tumor, reoccurrence and metastatic status. In 2017, the American Cancer Society (ACS) estimates that there will be about 255,180 new cases of breast cancer diagnosed in the United States (U.S.) and approximately 41,070 deaths from the disease.

Protein-bound paclitaxel was first approved by the U.S. Food and Drug Administration (FDA) in January 2005 for use as a single agent (monotherapy) for the treatment of breast cancer in individuals who have metastatic disease refractory to conventional combination chemotherapy or who have experienced relapse within 6 months of adjuvant chemotherapy; prior therapy in these individuals should have included an anthracycline antineoplastic agent (for example, doxorubicin) unless clinically contraindicated.

The current indication for use of protein-bound paclitaxel as a single agent in advanced breast cancer is based primarily on data from two single-arm open label studies (n=106) and a randomized, controlled, comparative study of 460 individuals with metastatic breast cancer. In

the single-arm open label studies, protein-bound paclitaxel was administered at doses of 175 mg/m^2 (n=43) and 300 mg/m^2 (n=63). Cycles were administered at 3-week intervals. Objective responses were observed in both studies. In the multicenter, randomized, open-label, phase III comparative trial, 460 participants with metastatic breast cancer were randomized 1:1 to receive protein-bound paclitaxel at a dose of 260 mg/m^2 intravenously (I.V.) over 30 minutes or standard paclitaxel at 175 mg/m^2 I.V. over 3 hours with premedication. At study entry, 64% of participants had an impaired ECOG Performance Status score of 1 or 2, 79% had visceral metastases and 76% had > 3 sites of metastases. A total of 14% of the participants did not receive prior chemotherapy, 27% received chemotherapy in the adjuvant setting, 40% in the metastatic setting, and 19% in both metastatic and adjuvant settings. Protein-bound paclitaxel was administered as second or > second-line therapy to 59% of participants, with 77% of participants previously exposed to anthracyclines. Participants in the protein-bound paclitaxel arm experienced a significantly higher response rate (RR) (the primary endpoint) compared with standard paclitaxel (33% vs. 19%, respectively; p=0.001) and significantly longer time to tumor progression (23.0 vs. 16.9 weeks, respectively; hazard ratio [HR], 0.75; p=0.006).

The most common adverse reactions (≥ 20%) with single-agent use of protein-bound paclitaxel were alopecia, neutropenia, sensory neuropathy, abnormal electrocardiogram, fatigue/asthenia, myalgia/arthralgia, aspartate aminotransferase (AST) elevation, alkaline phosphatase (ALP) elevation, anemia, nausea, infections, and diarrhea. Sensory neuropathy results in 3% of participants discontinuing treatment. Severe cardiovascular events possibly related to single-agent protein-bound paclitaxel occurred in 3% of participants.

Protein-bound paclitaxel has been utilized in the treatment of any breast cancer as a substitute for solvent-based paclitaxel when an individual experiences a documented allergic reaction. This recommendation is based, in part, on a black box warning on the FDA-approved label for solvent-based paclitaxel which states:

> Fatal anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving Taxol in clinical trials. Fatal reactions have occurred in patients despite premedication. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

The National Comprehensive Cancer Network® (NCCN) Clinical Practice Guideline (CPG) in Oncology for invasive breast cancer (recurrent or metastatic) (V2.2017) states albumin-bound paclitaxel may be used as single agent ("other") therapy for recurrent or metastatic breast cancer. In addition, albumin-bound paclitaxel may be used in preoperative/adjuvant therapy regimens or chemotherapy regimens for recurrent or metastatic breast cancer as a substitute "…for paclitaxel or docetaxel due to medical necessity (i.e., hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m^2."

Untch and colleagues (2016) evaluated the use of protein-bound paclitaxel compared with solvent-based paclitaxel in a neoadjuvant chemotherapy regimen in a phase III study (GeparSepto-GBG 69) of individuals with previously untreated unilateral or bilateral primary invasive breast cancer (subtype Ki67 and secreted protein acidic and rich in cysteine [SPARC]

expression). Participants were women ages 18 years or older with a Karnofsky Performance Status (KPS) index of at least 80%, tumor larger than 2 centimeters without additional risk factors, or between 1 and 2 centimeters (cT1c) with one of the following additional criteria: either clinical or pathological nodal involvement or hormone receptor-negative, or human epidermal growth factor receptor 2 (HER2)-positive, or Ki67 greater than 20%. Participants were randomly assigned to receive weekly protein-bound paclitaxel or weekly solvent-based paclitaxel, both followed by epirubicin plus cyclophosphamide. Participants with HER2-positive tumors received concurrent trastuzumab and pertuzumab every 3 weeks concomitantly with chemotherapy for all cycles. The primary endpoint was pathological complete response (CR), defined as no invasive or non-invasive tumor residuals in breast and axillary lymph nodes after neoadjuvant therapy. Of the 1229 women who were randomly assigned to treatment, a total of 1206 started treatment with protein-bound paclitaxel (n=606) and solvent-based paclitaxel (n=600). A preplanned safety analysis was performed after the sixtieth participant finished taxane therapy, after which time a decision was made to reduce the protein-bound paclitaxel dose due to an unacceptable increase in treatment discontinuation and sensory neuropathy in this group. A total of 444 (73%) participants in the protein-bound paclitaxel group and 477 (80%) in the solvent-based paclitaxel group (p=0.012) completed the taxane, epirubicin, and cyclophosphamide therapy. Pathological CR occurred more frequently in the protein-bound group (n=233 [38%]; 95% confidence [CI] 35-42 participants) than in the solvent-based paclitaxel group (n=174 [29%]; 95% CI, 25-33 participants) (odds ratio [OR] 1.53; 95% CI, 1.20-1.95 [unadjusted p=0.00065]). The incidence of grade 3-4 adverse events was significantly higher in the protein-bound paclitaxel group than in the solvent-based paclitaxel group for anemia (13 [2%] of 605 participants in the protein-bound group vs. 4 [1%] of 601 participants in the solvent-based paclitaxel group; p=0.048) and peripheral sensory neuropathy (63 [10%] participants receiving any protein-bound paclitaxel dose; 31 [8%] of participants starting with 125 mg/m² and 32 [15%] of participants starting with 150 mg/m² vs. 16 [3%] in the solvent-based paclitaxel group; p<0.001). At least one serious adverse event was observed in 283 (23%) participants (156 [26%] in the protein-bound paclitaxel group; 127 [21%] in the solvent-based paclitaxel group; (p=0.057). There were three deaths (during epirubicin plus cyclophosphamide treatment) in the protein-bound paclitaxel group (due to sepsis, diarrhea, and accident unrelated to the trial) compared with one death in the solvent-based paclitaxel group (cardiac failure during paclitaxel treatment). Limitations of this trial include the heterogeneous study population at baseline enrollment (by tumor type and central pathology) and the reduction in protein-bound paclitaxel dose to 125 mg/m² in approximately one-third of the enrolled study participants (resulting in less peripheral sensory neuropathy), although the investigators reported this dose reduction did not affect the frequency of pathological CR; therefore, the overall results for pathological CR are reflective of the lower protein-bound paclitaxel dose. In an exploratory analysis of this study, Furlanetto and colleagues (2017) reported dose reduction with protein-bound paclitaxel (125 mg/m^2) were associated with decreased toxicity rates (especially peripheral sensory neuropathy), without influencing pathological CR. A limitation of this analysis is the lack of randomization of participants to protein-bound paclitaxel at doses of 125 mg/m^2 or 150 mg/mg^2 at study onset, which limits direct comparisons of the long-term efficacy and safety of protein-bound paclitaxel use in the neoadjuvant setting. Additional randomized comparative trials are needed to evaluate the efficacy and safety of protein-bound paclitaxel, in terms of dosing and tolerability, as neoadjuvant chemotherapy in the treatment of early stage breast cancer.

Locally Advance or Metastatic Non-small Cell Lung Cancer (NSCLC)
NSCLC is any type of epithelial lung cancer other than SCLC, and is classified into 2 major types: squamous cell carcinoma, which accounts for 25% to 30% of all NSCLC cases and non-squamous cell carcinoma, the most common lung cancer in the U.S. When treatable, surgical resection with curative intent is the primary treatment for lung cancer. Chemotherapy may be used both preoperatively (neoadjuvant chemotherapy) and postoperatively (adjuvant chemotherapy) and as first-line for more advanced stages of lung cancer. In 2017, the ACS estimates there will be about 222,500 new cases of lung and bronchus cancer diagnosed in the U.S. and approximately 155,870 deaths from the disease.

In October 2012, protein-bound paclitaxel was approved by the FDA as first-line treatment of locally advanced or metastatic NSCLC, in combination with carboplatin, in individuals who are not candidates for curative surgery or radiation therapy. The FDA approval was based primarily on the results of a phase III, multicenter, randomized open-label study where individuals with advanced NSCLC received either protein-bound paclitaxel (100 mg/m^2) weekly plus carboplatin at under the concentration-time curve (that is, area under the curve [AUC]=6) every 3 weeks (n=521) or solvent-based (sb) (conventional) paclitaxel (200 mg/m^2) every 3 weeks plus carboplatin (AUC=6) (n=531). The study met its primary endpoint demonstrating a statistically significant objective response rate (ORR) for participants in the protein-bound paclitaxel arm compared to those in the sb-paclitaxel arm (33% vs. 25%; RR ratio, 1.313; 95% CI, 1.082 to 1.593; p=0.005). Protein-bound paclitaxel demonstrated a higher ORR as compared to sb-paclitaxel for squamous cell carcinoma histology (41% vs. 24%; RR ratio, 1.680; 95% CI, 1.271 to 2.221; p<0.001) and large cell carcinoma (33% vs. 15%); in addition, protein-bound paclitaxel achieved a similar ORR to sb-paclitaxel in individuals with adenocarcinoma (26% vs. 25%). There was approximately 10% improvement in progression-free survival (PFS) (median, 6.3 vs. 5.8 months; HR, 0.902; 95% CI, 0.767 to 1.060; p=0.214) and overall survival (OS) (OS median, 12.1 vs. 11.2 months; HR, 0.922; 95% CI, 0.797 to 1.066; p=0.271) in the protein-bound paclitaxel arm versus the sb-paclitaxel arm, respectively. North America study participants ≥ 70 years old showed a significantly increased OS with protein-bound paclitaxel compared to participants who received sb-paclitaxel.

Significantly less grade ≥ 3 neuropathy, neutropenia, arthralgia, and myalgia occurred in the protein-bound paclitaxel arm, and less thrombocytopenia and anemia occurred in the sb-paclitaxel arm. The most common adverse reactions (≥ 20%) when protein-bound paclitaxel was used in combination with carboplatin for NSCLC were alopecia, anemia, fatigue, nausea, neutropenia, peripheral neuropathy, and thrombocytopenia.

The NCCN CPG for NSCLC (V9.2017) includes a category 2A recommendation (based upon lower-level evidence and uniform NCCN consensus that the intervention is appropriate) for use of protein-bound paclitaxel in combination with platinum-based therapy for individuals with advanced, incurable NSCLC, stating "cisplatin or carboplatin have been proven effective in combination with many of the following agents..." including albumin-bound paclitaxel." In addition, the CPG includes a category 2A recommendation for use of protein-bound paclitaxel as a substitute for solvent-based paclitaxel or docetaxel stating, "Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity

reactions after receiving paclitaxel or docetaxel despite premedication, or for patients were the standard premedications (i.e., dexamethasone, H2 blockers, H1 blockers) are contraindicated)."

Metastatic Adenocarcinoma of the Pancreas

Adenocarcinoma of the pancreas is a tumor that metastasizes (spreads) within the abdomen to the liver, lungs, bone, and brain. These cancers cannot be removed by surgery. Chemotherapy is considered the primary treatment of adenocarcinoma of the pancreas, is not curative, but may shrink or slow the growth of these tumors. Rates of pancreatic cancer have been fairly stable over the past several years. In 2017, the ACS estimates there will be about 53,670 new cases of pancreas cancer diagnosed in the U.S. and approximately 43,090 deaths from the disease.

In September 2013, the FDA approved protein-bound paclitaxel for use in the treatment of metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine. Combination therapy has been associated with higher response rates and prolonged OS and PFS compared with single-agent gemcitabine. The clinical effectiveness of protein-bound paclitaxel was evaluated in a multicenter, multinational, randomized, open-label study comparing protein-bound paclitaxel plus gemcitabine to gemcitabine monotherapy as first-line treatment of metastatic adenocarcinoma of the pancreas. Study participants included those individuals with Karnofsky Performance Status (KPS) ≥ 70, normal bilirubin levels, transaminase levels ≤ 2.5 times the upper limit of normal (ULN) or ≤ 5 times the ULN for individuals with liver metastasis, no prior cytotoxic chemotherapy in the adjuvant setting or for metastatic disease, no ongoing active infection requiring systemic therapy, and no history of interstitial lung disease. A total of 861 participants were randomized (1:1) to receive protein-bound paclitaxel plus gemcitabine (n=431) or gemcitabine (n=430). Randomization was stratified by geographic region (Australia, Western Europe, Eastern Europe, or North America), KPS (70 to 80 vs. 90 to 100), and presence of liver metastasis (yes vs. no). In the intent-to-treat (all randomized) population, the median age was 63 years (range 27-88 years) with 42% ≥ 65 years of age and KPS was 90-100 in 60%. Disease characteristics included 46% of participants with 3 or more metastatic sites and 84% of participants with liver metastasis. Participants randomized to the protein-bound paclitaxel plus gemcitabine arm received 125 mg/m^2 I.V. infusion over 30-40 minutes followed by gemcitabine 1000 mg/m^2 I.V. infusion over 30-40 minutes on days 1, 8, and 15 of each 28-day cycle. Participants randomized to the gemcitabine arm received 1000 mg/m^2 I.V. infusion over 30-40 minutes weekly for 7 weeks followed by a 1-week rest period in Cycle 1, then as 1000 mg/m^2 on days 1, 8, and 15 of each subsequent 28-day cycle. Participants in both arms received treatment until disease progression or unacceptable toxicity. The primary outcome measure was OS; additional outcome measures were PFS and ORR. The median OS was 8.5 months in the protein-bound paclitaxel plus gemcitabine group compared to 6.7 months in the gemcitabine group (HR for death, 0.72; 95% CI, 0.62 to 0.83; p<0.001). The OS rate at 1 year was 35% in the protein-bound paclitaxel plus gemcitabine group compared to 22% in the gemcitabine group and 9% versus 4% at 2 years. The median PFS was 5.5 months in the protein-bound plus gemcitabine group compared to 3.7 months in the gemcitabine group (HR for disease progression or death, 0.69; 95% CI, 0.58 to 0.82; p<0.001); the ORR according to an independent reviewer was 23% versus 7% in the 2 groups (p<0.001). The most common adverse events of grade 3 or higher were neutropenia (38% in the protein-bound paclitaxel plus gemcitabine group vs. 27% in the gemcitabine group), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%). Febrile neutropenia occurred in 3% versus 1% of the

participants in the 2 groups. In the protein-bound paclitaxel plus gemcitabine group, neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 days. In exploratory analyses conducted in clinically relevant subgroups with a sufficient number of subjects, the treatment effects on OS were similar to that observed in the overall study population.

Goldstein and colleagues (2015) reported results of long-term survival with gemcitabine plus protein-bound paclitaxel in participants from the MPACT trial. A total of 3% of participants in the treatment arm were alive at 42 months, compared to no living participants in the control arm at that time. Factors that were associated with survival in the MPACT trial included KPS score and absence of liver metastases.

Malignant Melanoma

Melanoma is a malignant tumor of melanocytes, which are the cells that make the pigment melanin and are derived from the neural crest. Although most melanomas arise in the skin, they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate, including the uveal tract. Malignant melanoma of the skin is also referred to as cutaneous melanoma. Melanoma is the most common cancer in young adults aged 25 to 29 years and the second most common cancer in those aged 15 to 29 years. In 2017, the ACS estimates there will be about 87,110 new cases of melanoma of the skin diagnosed in the U.S. and approximately 9,730 deaths from the disease.

The NCCN CPG for melanoma (V1.2018) includes a category 2A recommendation for use of protein-bound (albumin-bound or nab-paclitaxel) paclitaxel as a cytotoxic regimen for metastatic disease ("Other Systemic Therapies"), although, "In general, options for front-line therapy for metastatic melanoma include immunotherapy or targeted therapy." The CPG recommendation is based on data from two phase II clinical trials where protein-bound paclitaxel yielded RR of 22% to 26% among chemotherapy-naïve individuals with metastatic melanoma.

Hersh and colleagues (2010) evaluated the effectiveness and safety of protein-bound paclitaxel in previously treated and chemotherapy-naive individuals with histologically or cytologically measureable metastatic melanoma. Protein-bound paclitaxel was administered weekly for 3 of 4 weeks at a dose of 100 mg/m^2 I.V. in previously-treated participants (n=37) or 150 mg/m^2 I.V. in chemotherapy-naïve participants (n=37). The RR was 2.7 % (1 of 37 participants; 95% CI, 0.1%-14.2%) in the previously treated arm and 21.6% (8 of 37 participants; 95% CI, 8.4%-34.9%) in chemotherapy-naïve participants. The duration of response for the previously treated participants was 12.9 months; for the chemotherapy-naïve participants, the median duration of response was 24.9 months. An additional 13 (35%) of the previously treated participants and 10 (27%) of the chemotherapy-naïve participants had stable disease for at least 16 weeks. The median PFS was 3.5 months (95% CI, 1.7-5.6 months) and 4.5 months (95% CI, 3.4-6.7 months), and the median OS was 12.1 months (95% CI, 6.5-17.5 months) and 9.6 months (95% CI, 6.7-23.7 months) in the previously treated and chemotherapy-naïve cohorts, respectively. Approximately 78% of the previously treated participants and 49% of the chemotherapy-naïve participants were treated without dose reduction. A total of 8 (22 %) chemotherapy-naïve participants discontinued therapy because of toxicity, usually neuropathy or myelosuppression. Grade 3 or 4 neutropenia was experienced by 41% and 14% of participants in the chemotherapy-naïve and previously

treated groups, respectively; additional treatment-emergent and treatment-related toxicities included alopecia, neuropathy, and fatigue.

Kottschade and colleagues (2011) evaluated the clinical effectiveness and safety of protein-bound paclitaxel in individuals with unresectable stage IV melanoma. The study consisted of two parallel phase II cohorts who were chemotherapy-naïve or previously treated. Eligible participants were ≥ 18 years of age with unresectable, histologically confirmed stage IV melanoma as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), ECOG Performance Status of 0 to 2, life expectancy ≥ 3 months, adequate hematologic and hepatic function, and ≥ 4 weeks since the last chemotherapy (previously treated cohort), radiation therapy, or immunotherapy. Treatment consisted of protein-bound paclitaxel administered by I.V. infusion at 100 mg/m^2 followed by carboplatin (with a target AUC of 2) administered over 30 minutes on days 1, 8, and 15 of a 28-day cycle. If participants did not develop excessive toxicity or progressive disease, treatment beyond 8 cycles was at the discretion of the treating physician. The primary endpoint was the ORR, defined as the number of eligible participants whose disease met RECIST criteria for response. For those participants whose disease responded to treatment, the duration of response was defined as "the time from the first tumor evaluation, when an objective status of complete response (CR) or partial response (PR) was assigned, to date of disease progression." A total of 76 participants (41 chemotherapy-naïve and 35 previously treated) were enrolled and 3 participants withdrew consent prior to starting treatment. The median number of treatment cycles administered was 4. Dose reductions and dose omissions were primarily related to severe neutropenia and neuropathy. A total of 28 individuals discontinued study participation due to disease progression, with 1 treatment-related death. There were 10 (25.6%) responses (1 CR and 9 PR) in the chemotherapy-naïve group (90% CI, 16.7% to 42.3%) and 3 (8.8%) responses (3 PR) in the previously treated (90% CI, 2.5% to 21.3%). Median PFS was 4.5 months in the chemotherapy-naïve cohort and 4.1 months in the previously treated group. Median OS was 11.1 months in the chemotherapy-naïve group and 10.9 months in the previously treated group. Severe toxicities in both groups (greater ≥ grade 3) included neutropenia, thrombocytopenia, neurosensory problems, fatigue, nausea, and vomiting

Ovarian Cancer (Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer)

According to the NCI (2017) epithelial carcinoma of the ovary is one of the most common gynecologic malignancies and the fifth most frequent cause of cancer death in women, with 50% of all cases occurring in women older than 65 years. Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasms (about 90%); however, less common pathologic subtypes may occur. In 2017, the ACS estimates there will be about 22,440 new cases of ovarian cancer diagnosed in the U.S. and approximately 14,080 deaths from the disease.

The NCCN CPG for ovarian cancer (including epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer) (V3.2017) includes a category 2A off-label recommendation for use of protein-bound paclitaxel when used as a single agent for persistent or recurrent disease. The recommendation is based in part on general consensus and data in the peer-reviewed medical literature including two phase II studies where an ORR of 64% was reported with use of single-agent protein-bound paclitaxel for recurrent ovarian cancer.

Teneriello and colleagues (2009) evaluated the effectiveness and safety of protein-bound paclitaxel in a phase II, open-label study of 47 individuals (44 evaluable participants) with recurrent platinum-sensitive, histologically or cytologically confirmed measurable epithelial cancer of the ovary, fallopian tube, or peritoneum cancer (any stage, grade 2 to 3 if stage I) according to RECIST or an elevated CA-125 (> 70 U/mL) in persons without measurable disease. Participants were administered protein-bound paclitaxel at 260 mg/m^2 I.V. for 30 minutes on day 1 of a 21-day cycle for 6 cycles or until disease progression. The median age of participants was 65.5 years; 76% had stage IIIC or IV disease, 81% had ECOG Performance Status of 0, and 94% had prior surgery. Treatment outcomes were assessed with RECIST, CA-125, or both methods (if applicable). The ORR was 64% (15 CR and 13 PR among 44 assessable participants). In participants evaluated with RECIST only, the ORR was 45% (CR, 1 of 11; PR, 4 of 11). In participants with only elevated CA-125, the ORR was 82% (CR, 7 of 11; PR, 2 of 11). In participants meeting both RECIST and CA-125 criteria, the ORR was 64% (CR, 7 of 22; PR, 7 of 22). The median time to response was 1.3 months (range, 0.5 to 4.8 months), the median duration of the best response was 7.9 months, and the estimated median PFS was 8.5 months. Two participants withdrew from the study because of neuropathy. The most frequent grade 3 to 4 treatment-related toxicities reported as "mild to moderate and manageable" were neutropenia (24%) and neuropathy (9%).

Coleman and colleagues (2011) evaluated the efficacy and safety of protein-bound paclitaxel in a phase II study of 51 individuals (47 evaluable participants) with platinum- and taxane-resistant ovarian cancer, defined as persistent or progressive disease following primary chemotherapy (n=5) or recurrence within 6 months of treatment completion (n=42). The median age of participants was 59 years (range, 34-78), 72% had serous histology, 81% had high-grade disease, and all participants had no prior therapy for recurrent disease and a Gynecologic Oncology Group Performance Status of ≤ 2. Protein-bound paclitaxel was administered at 100 mg/m² I.V. on days 1, 8, and 15 on a 28-day schedule. Treatment modifications, including dose reductions and a delay in therapy (for a maximum of 2 weeks), were allowed for hematologic toxicity based on absolute neutrophil counts (ANCs). Dose reductions and delay in subsequent therapy was allowed for specific grade 2 (or greater) non-hematologic toxicities. The primary endpoint was frequency of objective tumor response. Secondary endpoints included frequency and severity of adverse effects, and duration of PFS and OS. The median number of cycles administered was 4 (range, 1-40) and the most common reason for treatment discontinuation was disease progression occurring in 42 (82%) of participants. Treatment-associated toxicity, physician preference and participant preference accounted for an additional 3 (6%), 3 (6%) and 2 (4%) treatment discontinuations, respectively. Of the 47 evaluable participants, 1 CR and 10 PRs were confirmed (23%); 17 participants (36%) had stable disease. The median PFS was 4.5 months (95% CI, 2.2-6.7); OS was 17.4 months (95% CI, 13.2-20.8). A total of 17 participants (36%) had PFS > 6 months. There were no grade 4 toxicities observed; grade 3 toxicities included neutropenia (n=6), anemia (n=3), gastrointestinal (n=2), metabolic (n=2), pain (n=2), and leukopenia (n=1). Neurosensory toxicity was observed as grade 2 in 5 participants and grade 3 in 1 participant.

In the absence of a randomized controlled trial, the data from these two studies supports the NCCN 2A recommendation for use of single-agent protein-bound paclitaxel in a cohort of individuals with persistent or recurrent ovarian cancer.

Urothelial Carcinoma
Bladder cancers are divided into several types and may respond differently to treatments. More than 90% of bladder cancers are urothelial (transitional cell) carcinoma which occurs in the urinary tract system, involving the renal pelvis to the proximal urethra. According to the NCI (2017), bladder cancer is the sixth most common cancer in the U.S., the third most common cancer in men, but only the eleventh most common cancer in women. In 2017, the ACS estimates there will be about 79,030 new cases of bladder cancer diagnosed in the U.S. and approximately 16,870 deaths from the disease.

The NCCN CPG for bladder cancer (V5.2017) includes a category 2A recommendation for use of protein-bound paclitaxel as a single agent, subsequent systemic therapy, and an alternate regimen for select individuals with locally advanced or metastatic urothelial carcinoma of the bladder. The NCCN states "Data for subsequent-line systemic therapy for locally advanced or metastatic disease are highly variable" and recommend enrollment in a clinical trial. "The available options depend on what was offered as first line." The NCCN recommendation was based on outcomes of an open-label, single-group, two-stage, phase II study of 48 individuals who had documented progression on or within 12 months of a first-line platinum containing regimen for locally advanced or metastatic urothelial cancer. Participants received single agent protein-bound paclitaxel at 260 mg/m^2 I.V. every 3 weeks until disease progression or occurrence of unacceptable toxic effects. The primary endpoint was objective tumor response defined by a CR or PR according to RECIST criteria. Participants received a median of six cycles (range, 1 to 15). Of the 47 evaluable participants, 1 (2.1%) participant had a CR and 12 (25.5%) participants had PRs, resulting in an overall response of 27.7% (95% CI, 17.3-44.4). Median PFS was 6 months (95% CI, 3.9-8.5), and median OS was 10.8 months (5.8-16.9). The most frequently reported grade 3 or higher toxic effects were pain, fatigue, hypertension, joint pain, and neuropathy; no treatment-related deaths occurred. Limitations of this study include the small sample size and lack of a randomized control group.

In contrast to the reasonable tolerability profile and efficacy reported in the Ko (2013) trial of single agent protein-bound paclitaxel, Alva and colleagues (2014) reported that combination therapy of protein-bound paclitaxel with carboplatin and gemcitabine was poorly tolerated as first-line therapy in a high risk population of individuals with advanced urothelial cancer. Participants had confirmed metastatic, locally recurrent of advanced pure or mixed urothelial cancer, ECOG Performance Status of 0-2, no prior chemotherapy for current disease stage, and no taxane for greater than or equal to 1 year. Therapy consisted of protein-bound paclitaxel at 220 mg/m^2 with optional dose escalation to 260 mg/m^2 for subsequent cycles, with carboplatin AUC 5 on day 1 and gemcitabine on days 1 and 8 in 21-day cycles. Dose modifications in all three drugs to -1 and -2 levels were allowed for toxicity. The primary endpoint was overall response rate (CR+PR) by RECIST 1.0 criteria. Secondary endpoints were safety, PFS and OS. A total of 16 participants were enrolled due to poor accrual. Thirteen participants had metastatic disease, 3 participants were women, and the median age was 73.9 years (range 51.3-83). ECOG Performance Status was 0 in 4 (25.0%) and 1 in 11 (68.8%) participants. A total of 11 of 16 (68.8%) participants were removed from study protocol due to toxicity (severe cytopenias/myelosuppression), of which 7 participants began other therapies before progression was documented and 1 participant withdrew consent. The ORR included 1 (6.3%) participant

who had a confirmed PR response among the 15 evaluable participants. Two participants (13.3%) had unconfirmed PR. The median PFS was 11.2 months (95% CI, 2.0-11.2 months). Median OS was 13.1 months (95% CI, 9.8-19.6 months). The number of treatment cycles ranged from 1 to 8 with a median of 3. Median PFS follow-up was 5.1 months (range, 1-11.2 months) and median survival follow-up was 13.1 months (range, 2-21 months). The investigators noted that the hematologic toxicity encountered with combination therapy or protein-bound paclitaxel, carboplatin and gemcitabine in this trial was more severe than their clinical experience with the same combination in a neoadjuvant trial conducted concurrently at their institution, where all but 3 of the 26 participants received all three cycles intended with similar doses; however, the investigators suggested the neoadjuvant population with bladder cancer "is a much more robust group in terms of the ability to tolerate cytotoxic chemotherapy than advanced bladder cancer patients who have a greater burden of disease, inferior performance status and poor renal function." Limitations of this study include the small sample size and high withdrawal rate, which "…rendered pointless any attempt at assessment of the regimen's efficacy."

In summary, additional well-designed, controlled studies evaluating alternative dosing schedules for protein-bound paclitaxel compared with other chemotherapy regimens are needed to determine its net health benefit, as a single-agent or in combination therapy, for locally advanced or metastatic urothelial cancer.

Key Words:

Breast cancer, Non-small cell lung cancer (NSCLC), adenocarcinoma of the pancreas, Abraxane, paclitaxel- protein-bound, metastatic melanoma, ovarian cancer, bladder cancer

Approved for Governing Bodies

On January 7, 2005, the U.S. Food and Drug Administration approved paclitaxel protein-bound particles for injectable suspension, albumin-bound (Abraxane™, a trademark of American BioScience, Inc.) for treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy. Nanoparticle paclitaxel is also called paclitaxel albumin-stabilized nanoparticle formulation. Prior therapy should have included an anthracycline unless clinically contraindicated.

On October 11, 2012, the FDA approved paclitaxel protein-bound particles for injectable suspension, albumin-bound (ABRAXANE for Injectable Suspension; Abraxis Bioscience a wholly owned subsidiary of Celgene Corporation) for use in combination with carboplatin for the initial treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are not candidates for curative surgery or radiation therapy.

On September 6, 2013, the FDA approved paclitaxel protein-bound particles (albumin-bound) (Abraxane for injectable suspension, Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation), in combination with gemcitabine for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT Codes:

J9264 Injection, paclitaxel protein-bound particles, 1 mg

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