Paclitaxel Protein-Bound (Nab-paclitaxel) (ABRAXANE)

National Drug Monograph

October 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Nab-paclitaxel is an albumin-bound form of paclitaxel which works as an anti-microtubule agent by promoting microtubule assembly from tubulin dimers and stabilizing microtubules. Stabilizing microtubules prevents de-polymerization and causes an inhibition of the normal dynamic reorganization of the microtubules which is necessary for important interphase and mitotic functions in the cells.
Indication(s) Under Review in this document (may include off label)	Nab-paclitaxel is a microtubule inhibitor indicated for the treatment of[1]: • Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of completing adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. • Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. • Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine.
Dosage Form(s) Under Review	Intravenous powder for suspension, 100mg single-use vial for reconstitution
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Category D

Executive Summary	
Efficacy	• In patients with metastatic breast cancer, nab-paclitaxel, compared to conventional paclitaxel, demonstrated significantly higher response rates (33% vs. 19%, respectively) and longer time to progression (23.0 weeks vs. 16.9 weeks, respectively). Overall survival was similar in those receiving nab-paclitaxel as first-line therapy and significantly higher in those receiving as second-line or greater therapy when compared to standard paclitaxel. • When combined with carboplatin, nab-paclitaxel demonstrated significantly higher overall response rate compared to paclitaxel in patients with NSCLC (33% vs. 25%, respectively). With squamous histology, overall response rate was significantly higher with nab-paclitaxel compared to paclitaxel (41% vs. 24%, respectively), but was similar with non-squamous histology. Progression free survival and overall survival were non-inferior compared with paclitaxel. • In patients with advanced pancreatic cancer, overall survival (8.5 vs. 6.7 months),

<table>
<tr><td></td><td>progression free survival (5.5 vs. 3.7 months), and overall response rates (23% vs. 7%) were significantly improved in those receiving gemcitabine and nab-paclitaxel compared to single-agent gemcitabine.</td></tr>
<tr><td>Safety</td><td>• The most common adverse events include alopecia, sensory neuropathy, fatigue, neutropenia, myalgia/arthralgia, LFT elevation, anemia, nausea, vomiting, infections, diarrhea, thrombocytopenia, peripheral edema, and decreased appetite.
• Serious/life-threatening adverse events include severe neutropenia, severe neuropathy, severe infection (sepsis), severe pulmonary adverse effects, allergic/anaphylactic reaction
• Sensory neuropathy, neutropenia, arthralgia, and myalgia occurred significantly less often compared to paclitaxel.
• Peripheral neuropathy and myelosuppression were significantly increased when nab-paclitaxel was used in combination with gemcitabine for metastatic pancreatic cancer compared to gemcitabine monotherapy.</td></tr>
<tr><td>Other Considerations</td><td>
<table>
<tr><td>Outcome in clinically significant area</td><td>Breast cancer: ORR, PFS, OS vs paclitaxel
NSCLC: ORR, PFS, OS vs paclitaxel/carboplatin
Pancreatic cancer: OS, PFS, ORR vs gemcitabine</td></tr>
<tr><td>Effect Size</td><td>Breast cancer: ORR 33% [95% CI 27.09-39.29]; PFS 23 weeks [HR 0.75]; OS 65 weeks
NSCLC: ORR 33% [95% CI 1.085-1.593]; PFS 6.3 months [HR 0.902, 95% CI 0.767-1.060]; OS 12.1 months [HR 0.922, 95% CI 0.797-1.066]
Pancreatic cancer: OS 8.5 months [HR 0.72, 95% CI 0.62-0.83]; PFS 5.5 months [HR 0.69, 95% CI 0.58-0.82]; ORR 23% [95% CI 2.18-4.66]</td></tr>
<tr><td>Potential Harms</td><td>Breast cancer: ≥ 20% alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea
NSCLC: ≥ 20% anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, fatigue. Serious: anemia (4%) and pneumonia (3%)
Pancreatic cancer: ≥ 20% neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, dehydration. Serious: pyrexia (6%), dehydration (5%), pneumonia (4%), vomiting (4%)</td></tr>
<tr><td>Net Clinical Benefit</td><td>Breast cancer: Minimal (low benefit, low risk of harm)
NSCLC: Minimal (low benefit, low risk of harm)
Pancreatic cancer: Moderate (high benefit, high risk of harm)</td></tr>
</table>
• Vials should be stored in original cartons at 20°C to 25°C (68°F to 77°F) and retained in the original package to protect from bright light.
• Neither freezing or refrigeration adversely affects the stability of the product
• Reconstituted product in the vial should be used immediately but may be refrigerated at 2°C to 8°C (36°F to 46°F) for a maximum of 24 hours if necessary. If not used immediately, reconstituted suspension should be replaced in the original carton to protect it from bright light.
• The suspension for infusion when prepared as recommended in an infusion bag should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from bright light for a maximum of 24 hours
• The total combined refrigerated storage time of reconstituted product in the vial and in the infusion bag is 24 hours
• Reconstituted nab-paclitaxel can be injected in PVC or non-PVC type</td></tr>
</table>

	intravenous bags or containers. The use of DEHP-free solution containers or administration sets is not necessary to prepare or administer nab-paclitaxel infusions. • The use of medical devices such as silicone oil as a lubricant (i.e. syringes and intravenous bags) to reconstitute and administer nab-paclitaxel may result in the formation of proteinaceous strands, which should be discarded if observed on visual inspection. • Pre-medication with corticosteroids and antihistamines to reduce the incidence of severe hypersensitivity reactions is not needed
Potential Impact	• In metastatic breast cancer, nab-paclitaxel monotherapy may be used in place of paclitaxel monotherapy as second-line or greater therapy. The NCCN classifies the use of nab-paclitaxel as a Category 2A recommendation in this indication. • In NSCLC, nab-paclitaxel may be used in combination with carboplatin as first-line therapy in place of combination paclitaxel and carboplatin. The NCCN classifies the use of nab-paclitaxel as a Category 2A recommendation in this indication. o Nab-paclitaxel is given weekly with carboplatin every 21 days compared to paclitaxel, which can be given every 3 weeks (or weekly). This may be less convenient for some patients due to weekly treatments and no break between cycles. • In metastatic pancreatic cancer, nab-paclitaxel may be used in combination with gemcitabine as first-line therapy. The NCCN classifies the use of both the combination and gemcitabine monotherapy as Category 1 recommendations in the first-line setting for this indication. • Nab-paclitaxel may be associated with less sensory neuropathy compared to paclitaxel.

Background

Purpose for review

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating nab-paclitaxel for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Issues to be determined:

✔ Evidence of need
✔ Does nab-paclitaxel offer advantages to currently available alternatives?
✔ What safety issues need to be considered?
✔ Does nab-paclitaxel have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Metastatic breast cancer monotherapy after failure of combination therapy

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance
docetaxel	Given intravenously. Can be dosed every 3 weeks or weekly. Dosing every 3 weeks resulted in an improvement in disease-free survival compared to weekly dosing. Can be associated with significant fluid retention, which can be reduced by premedication with dexamethasone	
paclitaxel	Given intravenously. Can be dosed weekly or every 3 weeks. Weekly dosing resulted in an improvement	

	in overall survival compared to every 3 week treatment. Infusion reaction is common with paclitaxel, and can be reduced by premedication with H1/H2 antagonists and dexamethasone. Risk of neuropathy is greater with paclitaxel compared to either docetaxel or nab-paclitaxel.	
doxorubicin	Given intravenously. Can be dosed weekly or every 3 weeks. Risk of cumulative cardiac toxicity. Potent vesicant.	
capecitabine	Given orally. Dosed twice daily for 14 days followed by 7 days of rest. Primary toxicities are hand-foot syndrome and diarrhea.	CFU available. In metastatic breast cancer: restricted for use in combination with docetaxel after failure of prior anthracycline-containing therapy or as monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen
vinorelbine	Given intravenously on days 1 and 8 every 21 days.	
gemcitabine	Given intravenously on days 1 and 8 every 21 days. Thrombocytopenia can be a dose limiting toxicity.	
Non-formulary Alternative (if applicable)	**Other Considerations**	
pegylated liposomal doxorubicin	Given intravenously every 4 weeks. Risk of cumulative cardiac toxicity.	
eribulin	Given intravenously on days 1 and 8 every 21 days. Primary toxicity includes neutropenia and peripheral neuropathy.	
ixabepilone	Given intravenously every 21 days. May have less activity compared with taxanes, but resulted in less hematologic toxicities.	
ado-trastuzumab	Only for HER-2 positive disease after progression on a trastuzumab-containing regimen	CFU available. Restricted for those with prior treatment with trastuzumab and a taxane separately or in combination, patients should have received prior therapy for metastatic breast cancer or developed disease recurrence during or within 6 months of completing adjuvant therapy

Locally advanced or metastatic NSCLC in combination with carboplatin

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance
carboplatin + paclitaxel	Carboplatin given intravenously every 3-4 weeks, paclitaxel can be given every 3 weeks (21 day cycle) or weekly x 3 (28 day cycle)	
carboplatin + docetaxel	Given intravenously every 3 weeks	
carboplatin + gemcitabine	Carboplatin given intravenously on day 1, gemcitabine given weekly x 2 every 3 weeks	

carboplatin + pemetrexed	Given intravenously every 3 weeks only for non-squamous NSCLC. Need vitamin supplementation (folic acid and vitamin B12)	
Non-formulary Alternative (if applicable)	**Other Considerations**	
carboplatin + paclitaxel + bevacizumab	Given intravenously every 3 weeks. The addition of bevacizumab was associated with a significant increase in objective response rate, overall survival, and progression free survival.	CFU available for bevacizumab, restricted for use in combination with a 2-drug chemotherapy regimen containing a platinum-based drug for stage IIIB or IV without prior therapy for advanced disease

First line treatments for metastatic pancreatic adenocarcinoma

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance
FOLFIRINOX (5-FU + leucovorin + irinotecan + oxaliplatin)	Preferred regimen for those with good performance status. Associated with significant toxicities such as diarrhea, fatigue, neutropenia, sensory neuropathy	
gemcitabine monotherapy	For patients who are not candidates for a more intensive first-line chemotherapy regimen.	

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to August 2015) using the search terms nab-paclitaxel, Abraxane and ABI-007. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Metastatic Breast Cancer

Trial	Treatment Groups	Outcomes	Results	Statistics
Gradishar et al[2] Metastatic breast cancer who are candidates for single-agent paclitaxel, had not received paclitaxel or docetaxel for metastatic disease	ABI-007 260 mg/m^2 21-day cycles (n=229) Paclitaxel 175 mg/m^2 21-day cycles (n=225) Assessments at baseline, weeks 5, 9, 15,	Primary: ORR Secondary: TTP, OS	**ORR** ABI-007: 33%, 95% CI (27.09-39.29) Paclitaxel: 19%, 95% CI (13.58-23.76) **TTP** ABI-007: 23.0 weeks Paclitaxel: 16.9 weeks **OS** ABI-007: 65.0 weeks	P = 0.001 HR 0.75 P = 0.006 P = 0.374

	and at end of treatment		Paclitaxel: 55.7 weeks **Duration of treatment** ABI-007: ≥ 6 cycles given to 129 patients (56%) Paclitaxel: ≥ 6 cycles given to 112 patients (50%)	
Rugo et al[3] Advanced breast cancer (stage IIIC or IV) who have not received prior chemotherapy for metastatic disease	Paclitaxel 90 mg/m^2 + bevacizumab 10 mg/kg Days 1,8,15 every 28 days (n=275) Nab-paclitaxel 150 mg/m^2 Days 1,8,15 every 28 days* (n=267) Ixabepilone 16 mg/m^2 Days 1,8,15 every 28 days* (n=241) *Nab-paclitaxel and ixabepilone dose schedules were altered to weekly administration for direct comparison to weekly paclitaxel Duration of treatment = 6 cycles	Primary: PFS Secondary: OS, ORR, TTF	**PFS** Paclitaxel + bevacizumab: 11 months Nab-paclitaxel: 9.3 months Ixabepilone: 7.4 months	Paclitaxel + bevacizumab vs. nab-paclitaxel HR 1.20 (95% CI 1.00-1.45; P = 0.054) Paclitaxel + bevacizumab vs. ixabepilone HR 1.59 (95% CI 1.31-1.93; P < 0.001)
			OS Paclitaxel + bevacizumab: 26.5 months vs. nab-paclitaxel: 23.5 months Paclitaxel + bevacizumab: 27.3 months vs. ixabepilone: 23.6	Paclitaxel + bevacizumab vs. nab-paclitaxel HR 1.17; (95%CI 0.92-1.47; P = 0.20) Paclitaxel + bevacizumab vs. ixabepilone HR 1.31; (95%CI 1.03-1.66; P = 0.027)
			ORR Paclitaxel + bevacizumab: 38% Nab-paclitaxel: 34% Ixabepilone: 27%	Paclitaxel + bevacizumab vs. nab-paclitaxel OR 0.84; P = 0.33 Paclitaxel + bevacizumab vs. ixabepilone OR 0.57; P = 0.0038
			TTF Paclitaxel + bevacizumab: 6.6 months vs. nab-paclitaxel: 5.2 months Paclitaxel + bevacizumab: 6.8 months vs.ixabepilone: 4.9 months	Paclitaxel + bevacizumab vs. nab-paclitaxel P < 0.001 Paclitaxel + bevacizumab vs. ixabepilone P < 0.001

ORR=objective response rate; TTP=time to tumor progression; OS=overall survival, PFS=progression free survival, TTF=time to treatment failure

- The FDA approval of nab-paclitaxel for the treatment of metastatic breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of completing adjuvant chemotherapy was

based on two single arm, open-label studies (N=106) showing objective responses and one multicenter randomized trial

- The phase III multicenter trial that lead to FDA approval was conducted in 460 patients with metastatic breast cancer who were candidates for single-agent paclitaxel therapy, had not received paclitaxel or docetaxel for metastatic disease, and had not relapsed with metastatic disease within 1 year of adjuvant paclitaxel or docetaxel treatment
- Participants were randomized to receive either nab-paclitaxel 260mg/m^2 intravenously over 30 minutes without corticosteroids or antihistamine premedication or paclitaxel 175mg/m^2 intravenously over 3 hours with premedication
- Nab-paclitaxel was found to have a significantly higher ORR compared to paclitaxel
- Nab-paclitaxel was associated with a statistically longer duration of TTP and OS compared to paclitaxel in those receiving nab-paclitaxel as second-line or greater therapy, but not in first line therapy
    - TTP in those receiving nab-paclitaxel as second-line or greater therapy was 20.9 weeks with ABI-007 vs. 16.1 weeks with paclitaxel (HR 0.73, P = 0.020).
    - OS in those receiving nab-paclitaxel as second-line or greater therapy was 56.4 weeks with ABI-007 vs. 46.7 weeks with paclitaxel (HR 0.73, P = 0.024).
- This study was supported by American BioScience, Inc.
- In the phase III study by Rugo in the first-line setting, nab-paclitaxel did not improve PFS or OS compared to paclitaxel/bevacizumab.
- In the study by Rugo et al, nab-paclitaxel was found to have significantly worse hematologic (22% vs. 55%, respectively) and non-hematologic toxicities (49% vs. 65% respectively) compared to paclitaxel (P < 0.001 for both)
    - Most common grade 3-4 hematologic toxicities were neutropenia and anemia
    - Most common grade 3-4 non-hematologic toxicities were sensory neuropathy, fatigue, hypertension, motor neuropathy, pain, and nausea
- This study was sponsored by National Cancer Institute (Alliance for Clinical Trials in Oncology, Alliance Data Center, and Breast Cancer Research Foundation.
- As requested by the FDA upon nab-paclitaxel's approval for metastatic breast cancer, a statement regarding no statistical significance found in OS was added to the package insert. Additionally, dose adjustments for hepatic impairment were subsequently reported in the package insert at the request of the FDA based on lack of consideration on the safety and pharmacokinetics of nab-paclitaxel in hepatically-impaired patients, which is relevant since the active ingredient, paclitaxel, is metabolized by the liver
- Evidence Grade: Moderate

First line therapy for locally advanced or metastatic non-small cell lung cancer[4]	**Nab-paclitaxel (N=521)**	**Paclitaxel (n=531)**	**Statistics**
Primary outcome			
ORR	33%	25%	Response rate ratio = 1.313 95% CI (1.085-1.593) P = 0.005
Squamous subset	41%	24%	Response rate ratio = 1.680 95% CI (1.271-2.221) P < 0.001
Non-squamous subset	26%	25%	Response rate ratio = 1.034 95% CI (0.788-1.358) P = 0.808
Secondary outcomes			
PFS	6.3 months 95% CI (5.6-7.0 months)	5.8 months 95% CI (5.6-6.7 months)	HR = 0.902 95% CI (0.767-1.060)

			P = 0.214
OS	12.1 months 95% CI (10.8-12.9 months)	11.2 months 95% CI (10.3-12.6 months)	HR = 0.922 95% CI (0.797-1.066) P = 0.271

ORR=objective response rate; PFS=progression free survival; OS=overall survival

- The FDA approval of nab-paclitaxel for use in combination with carboplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC was based on a multicenter randomized trial
- This multicenter trial was conducted in 1,052 untreated patients with non-resectable stage IIIB to IV NSCLC.
- Participants were randomized to receive nab-paclitaxel 100mg/m^2 intravenously over 30 minutes on days 1, 8, and 15 followed by carboplatin AUC 6 mg/mL/min on day 1 every 3 weeks or paclitaxel 200mg/m^2 intravenously over 3 hours plus carboplatin AUC 6 mg/mL/min both given every 3 weeks.
- Nab-paclitaxel was found to have a significantly higher ORR compared to paclitaxel. The benefits were significantly higher in the squamous subset, but not statistically different in the non-squamous subset.
- The PFS and OS in those receiving nab-paclitaxel were non-inferior compared to paclitaxel.
- In a study on an elderly subset of patients in the phase III advanced NSCLC trial, progression free survival trended in favor of nab-paclitaxel in elderly patients who were ≥ 70 years old (median 8.0 vs. 6.8 months, HR 0.687, p = 0.009).[5] In this subset, overall survival was found to be significantly improved (median 19.9 vs 10.4 months, HR 0.583, p = 0.009). Adverse events were similar in both age groups. Nab-paclitaxel was associated with less neutropenia (p = 0.015), neuropathy (p = 0.001), and arthralgia (p = 0.029), but increased anemia (p = 0.007).
- In an analysis of patient-reported neuropathy and taxane-associated symptoms from the phase III advanced NSCLC trial, patients receiving nab-paclitaxel reported significantly less worsening of peripheral neuropathy (p < 0.001), pain (p < 0.001), and hearing loss (p = 0.002).[6]
- Study was supported by Celgene
- Evidence Grade: Moderate

Metastatic pancreatic adenocarcinoma[7]

	Nab-paclitaxel plus gemcitabine (N=430)	**Gemcitabine (n=431)**	**Statistics**
Primary outcome			
OS	8.5 months 95% CI (7.89-9.53 months)	6.7 months 95% CI (6.01-7.23 months)	HR = 0.72 95% CI (0.62-0.83) P < 0.001
6-month survival	67% 95%CI (62-71)	55% 95% CI 50-60)	P < 0.001
1 year survival	35% 95%CI (30-39)	22% 95%CI (18-27)	P < 0.001
2-year survival	9% 95%CI (6-13)	4% 95%CI (2-7)	P = 0.02
Secondary outcomes			
PFS	5.5 months 95% CI (4.5-5.9 months)	3.7 months 95% CI (3.6-4.0 months)	HR = 0.69 95% CI (0.58-0.82) P < 0.001
ORR	23% 95% CI (19-27)	7% 95% CI (5-10)	Response rate ratio = 3.19 95% CI (2.18-4.66)

			P < 0.001
Treatment Duration	3.9 months (range 0.1-21.9)	2.8 months (range 0.1-21.5)	
	≥ 6 months treatment 32%	≥ 6 months treatment 15%	

OS=overall survival; PFS=progression free survival; ORR=objective response rate

- The FDA approval of nab-paclitaxel for use in combination with gemcitabine for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas was based on a multicenter, international, open-label randomized trial
- This trial was conducted in 861 untreated patients with metastatic pancreatic adenocarcinoma.
- Participants were randomized to receive nab-paclitaxel 125mg/m^2 intravenously over 30-40 minutes followed by gemcitabine 1000mg/m^2 on days 1, 8, 15, 29, 36, and 43 or gemcitabine alone 1000mg/m^2 weekly for 7 of 8 weeks (cycle 1). In subsequent cycles, all patients were administered treatment on days 1,8,15 every 4 weeks.
- Nab-paclitaxel and gemcitabine combination therapy was found to have a significantly longer OS and PFS, and higher ORR compared to gemcitabine monotherapy
- In an update report of OS based on longer follow-up, the median OS was significantly longer for nab-paclitaxel plus gemcitabine vs. gemcitabine alone (8.7 vs. 6.6 months, HR 0.72, 95% CI 0.62-0.83, P < 0.001).[8] Long-term (> 3-year) survivors were identified in the nab-paclitaxel plus gemcitabine arm only (4%). In poor-prognosis subgroups, there was a treatment effect for OS favoring nab-paclitaxel plus gemcitabine over gemcitabine alone (HR 0.612, P < 0.001 for CA19-9 level ≥ median and HR 0.81, P = 0.079 for neutrophil-to-lymphocyte ratio > 5)
- OS in FOLFIRINOX studied in a trial with a similar population was found to be significantly improved compared to gemcitabine monotherapy (11.1 months vs. 6.8 months, respectively, HR 0.57; 95% CI 0.45-0.73, P < 0.001).[9]
- An indirect comparison between FOLFIRINOX and gemcitabine/nab-paclitaxel may suggest a slightly greater activity but higher toxicity of FOLFIRINOX.
- This study was supported by Celgene
- Evidence Grade: High

Potential Off-Label Uses

- Head and neck cancer[10]
- First line treatment as monotherapy for metastatic breast cancer [2,11] (ORR was improved in the first-line setting but not statistically significant)
- First line treatment for advanced or metastatic NSCLC in combination with carboplatin and bevacizumab[12]
- Metastatic melanoma[13,14]
- Recurrent ovarian, fallopian tube, or primary peritoneal carcinomas[15]
- Second line for metastatic pancreatic cancer[7] (could be considered if patient fails first line therapy for metastatic pancreatic cancer with FOLFIRINOX)

Clinical trials with nab-paclitaxel are ongoing in the following areas:

- Gastrointestinal neuroendocrine carcinomas
- HPV-related oropharyngeal cancer
- Esophageal cancer

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• Warning: neutropenia. Do not administer nab-paclitaxel therapy to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. It is recommended that frequent peripheral blood cell counts be performed to

	monitor the occurrence of bone marrow suppression • Do not substitute for or with other paclitaxel formulations.
Contraindications	• Neutrophil counts of < 1,500 cells/mm^3 • Severe hypersensitivity reaction to nab-paclitaxel
Warnings/Precautions	• Causes myelosuppression, monitor CBC and withhold and/or reduce the dose as needed • Sensory neuropathy occurs frequently and may require dose reduction or treatment interruption. • Sepsis: In combination with gemcitabine: interrupt both until sepsis resolves and if neutropenic, until neutrophils are at least 1500 cells/mm^3, then resume treatment at reduced dose levels • Pneumonitis occurred with use of nab-paclitaxel in combination with gemcitabine; permanently discontinue treatment with both agents • Severe hypersensitivity reactions with fatal outcomes have been reported. Do not re-challenge with this drug • Exposure and toxicity of nab-paclitaxel can be increased in patients with hepatic impairment, therefore administer with caution • Contains albumin derived from human blood, which has theoretical risk of viral transmission • Fetal harm may occur when administered to a pregnant woman. Advise women of childbearing potential to avoid becoming pregnant while receiving • Advise men not to father a child while on nab-paclitaxel

Safety Considerations

- Overall safety profile of nab-paclitaxel in the clinical trials were similar to that of paclitaxel, with overall less incidence and quicker resolution of sensory neuropathy

Adverse Reactions

Common adverse reactions	Metastatic breast cancer incidence $\geq$ 20%: alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia, arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infection, and diarrhea. NSCLC incidence $\geq$ 20%: anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, fatigue. Pancreatic adenocarcinoma incidence $\geq$ 20%: fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, dehydration.
Death/Serious adverse reactions	Metastatic breast cancer: grade 4 neutropenia (9% vs. 22% with paclitaxel), cardiovascular (3%) included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension, cases of cerebrovascular attacks and transient ischemic attacks have been reported, grade 3 peripheral neuropathy (10%), severe ocular/vision disturbances (keratitis and blurred vision, received higher doses than recommended, reversible) (1%), grade 3 or 4 elevations in GGT (14% vs. 10% with paclitaxel), severe creatinine elevation (1%). NSCLC Grade 3 or 4: anemia (28% vs. 7% with paclitaxel), neutropenia (47% vs. 58% with paclitaxel), thrombocytopenia (18% vs. 9% with paclitaxel), peripheral neuropathy (3% vs. 12% with paclitaxel), arthralgia (<1% vs. 2% with paclitaxel), myalgia (<1% vs. 2% with paclitaxel), one treatment death in each arm (nab-paclitaxel and paclitaxel). Pancreatic adenocarcinoma Grade 3 or 4: neutropenia (38% vs. 27% with gemcitabine), thrombocytopenia (13% vs. 9% with gemcitabine), fatigue (18%

	vs. 9% with gemcitabine), peripheral edema (3% vs. 3% with gemcitabine), pyrexia (3% vs. 1% with gemcitabine), asthenia (7% vs. 4% with gemcitabine), mucositis (1% vs. <1% with gemcitabine), nausea (6% vs. 3% with gemcitabine), diarrhea (6% vs.1% with gemcitabine), vomiting (6% vs. 4% with gemcitabine), alopecia (1% vs. 0% with gemcitabine), rash (2% vs. <1% with gemcitabine), peripheral neuropathy (17% vs. 1% with gemcitabine), headache (<1% vs. <1% with gemcitabine), decreased appetite (5% vs. 2% with gemcitabine), dehydration (7% vs. 2% with gemcitabine), hypokalemia (4% vs. 1% with gemcitabine), epistaxis (<1% vs. <1% with gemcitabine), urinary tract infection (2% vs. <1% with gemcitabine), pain in extremity (1% vs. 1% with gemcitabine), arthralgia (1% vs. <1% with gemcitabine), myalgia (1% vs. 0% with gemcitabine), and depression (<1% vs. 0% with gemcitabine). Post-marketing reports: severe and sometimes fatal hypersensitivity reactions have been reported; reports of congestive heart failure, left ventricular dysfunction, and atrioventricular block mostly in those previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history; reports of pneumonitis, interstitial pneumonia, pulmonary embolism, radiation pneumonitis in patients receiving concurrent radiotherapy, and lung fibrosis; cranial nerve palsies, vocal cord palsies, and autonomic neuropathy; persistent optic nerve damage and cystoid macular edema with improvement after cessation of treatment; intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis; extravasation; generalized maculopapular rash, erythema, pruritus, photosensitivity reactions radiation recall phenomenon, palmar-plantar erythrodysesthesia in those previously exposed to capecitabine, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.
Discontinuations due to adverse reactions	Breast cancer: sensory neuropathy (3%), peripheral neuropathy (8%) NSCLC: neutropenia (3%), thrombocytopenia (3%), peripheral neuropathy (1%) Pancreatic cancer: neuropathy (8%), fatigue (4%), thrombocytopenia (2%)

Drug Interactions

Drug-Drug Interactions

- Metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4, use caution when concomitantly administering with inhibitors or inducers of either CYP2C8 or CYP3A4

Risk Evaluation

As of September 2015:

	Comments
Sentinel event advisories	• Sources: ISMP[16] • ISMP Medication Safety Alert (March 10, 2005) notes potential name confusion with nab-paclitaxel and paclitaxel

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Paclitaxel (protein bound) 100mg Inj Sus Abraxane	Paclitaxel Paxil Taxol Taxotere	Docetaxel None	Paclitaxel None	Pemetrexed Altabax

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

Outcome in clinically significant area	Breast cancer: ORR, PFS, OS NSCLC: ORR, PFS, OS Pancreatic cancer: OS, PFS, ORR
Effect Size	Breast cancer: ORR 33% [95% CI 27.09-39.29]; PFS 23 weeks [HR 0.75]; OS 65 weeks NSCLC: ORR 33% [Response rate ratio 1.313, 95% CI 1.085-1.593]; PFS 6.3 months [HR 0.902, 95% CI 0.767-1.060]; OS 12.1 months [HR 0.922, 95% CI 0.797-1.066] Pancreatic cancer: OS 8.5 months [HR 0.72, 95% CI 0.62-0.83]; PFS 5.5 months [HR 0.69, 95% CI 0.58-0.82]; ORR 23% [Response rate ratio 3.19, 95% CI 2.18-4.66]
Potential Harms	Breast cancer: $\geq$ 20% alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea NSCLC: $\geq$ 20% anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, fatigue. Serious: anemia (4%) and pneumonia (3%) Pancreatic cancer: $\geq$ 20% neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, dehydration. Serious: pyrexia (6%), dehydration (5%), pneumonia (4%), vomiting (4%)
Net Clinical Benefit	Breast cancer: Minimal (low benefit, low risk of harm) NSCLC: Minimal (low benefit, low risk of harm) Pancreatic cancer: Moderate (high benefit, high risk of harm)

- Vials should be stored in original cartons at 20°C to 25°C (68°F to 77°F) and retained in the original package to protect from bright light.
- Neither freezing or refrigeration adversely affects the stability of the product
- Reconstituted product in the vial should be used immediately but may be refrigerated at 2°C to 8°C (36°F to 46°F) for a maximum of 24 hours if necessary. If not used immediately, reconstituted suspension should be replaced in the original carton to protect it from bright light.
- The suspension for infusion when prepared as recommended in an infusion bag should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from bright light for a maximum of 24 hours
- The total combined refrigerated storage time of reconstituted product in the vial and in the infusion bag is 24 hours
- Reconstituted nab-paclitaxel can be injected in PVC or non-PVC type intravenous bags or containers. The use of DEHP-free solution containers or administration sets is not necessary to prepare or administer nab-paclitaxel infusions.
- The use of medical devices such as silicone oil as a lubricant (i.e. syringes and intravenous bags) to reconstitute and administer nab-paclitaxel may result in the formation of proteinaceous strings, which should be discarded if observed on visual inspection.
- Pre-medication with corticosteroids and antihistamines to reduce the incidence of severe hypersensitivity reactions is not needed

Dosing and Administration[1]

- Metastatic Breast Cancer: Recommended dosage of nab-paclitaxel is 260 mg/m^2 intravenously over 30 minutes every 3 weeks.

- Non-Small Cell Lung Cancer: Recommended dosage of nab-paclitaxel is 100 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle; administer carboplatin on Day 1 of each 21-day cycle immediately after nab-paclitaxel.
- Adenocarcinoma of the Pancreas: Recommended dosage of nab-paclitaxel is 125 mg/m^2 intravenously over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle; administer gemcitabine on Days 1, 8, and 15 of each 28-day cycle immediately after nab-paclitaxel.
- Refer to the package insert for full dosing information for dose modifications for patients with hepatic impairment, hematologic, neurologic, cutaneous, or gastrointestinal toxicities.
- Closely monitor the infusion site for extravasation and infiltration. No premedication is required prior to administration.

Special Populations (Adults)[1]

	Comments
Elderly	• No notable toxicities occur more frequently in patients with metastatic breast cancer ≥ 65 years (13% of patients) and ≥ 75 years (< 2 % of patients) • In a subsequent pooled analysis in metastatic breast cancer patients, a higher incidence of epistaxis, diarrhea, dehydration, fatigue, and peripheral edema was found in patients ≥ 65 years (15%) and ≥ 75 years (2%) • Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients with non-small cell lung cancer ≥ 65 years (31%) and ≥ 75 years (2%) • In patients with pancreatic adenocarcinoma; diarrhea, decreased appetite, dehydration, and epistaxis were more frequent in patients ≥ 65 years (41%) and ≥ 75 years (3.5%). No overall differences in effectiveness were observed
Pregnancy	• Pregnancy category D. Based on mechanism of action and findings in animals can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while receiving this drug. If used during pregnancy, or if the patient becomes pregnant while this receiving this drug, apprise patient of the potential hazard to the fetus.
Lactation	• It is not known whether paclitaxel is excreted in human milk. Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Renal Impairment	• Dose adjustment is not required for patients with mild to moderate renal impairment (estimated CrCl ≥ 30 to < 90 mL/min). Insufficient data to permit dosage recommendations in patients with severe renal impairment or end stage renal disease (estimated CrCl < 30 mL/min).
Hepatic Impairment	• The exposure of paclitaxel may be higher in patients with hepatic impairment. Dose reductions are indicated in patients with moderate to severe hepatic impairment. Refer to the package insert for full dosing information for dose modifications for patients with hepatic impairment.
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- FDA-approved uses include:
  - Metastatic 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
  - Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy
  - Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine

- Metastatic breast cancer
  - ORR and PFS benefit, but no OS benefit
  - Multiple other options available in this setting
  - No advantageous role for nab-paclitaxel except for patients unable to tolerate paclitaxel
- NSCLC
  - Only ORR benefit, but no PFS or OS benefit
  - Multiple other options available in this setting
  - No advantageous role for nab-paclitaxel except for patients unable to tolerate paclitaxel
- Metastatic pancreatic cancer
  - Improvement in OS, ORR, and PFS
  - Recommend nab-paclitaxel + gemcitabine in the first line setting for those who are not a candidate to receive FOLFIRINOX

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.