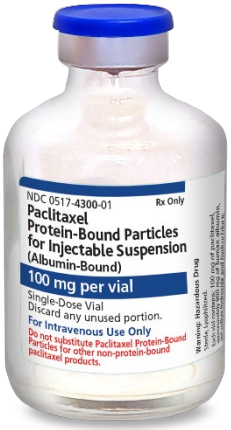
American Regent® Launches Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)



Supplied as a 100 mg single-dose vial.

Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) will provide new options for the availability of Albumin-Bound Paclitaxel to treat patients with certain types of cancer

Melville, NY – May 2, 2023: American Regent, Inc.® is pleased to announce the launch of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), which is an alternative to Abraxane®.

"The addition of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) to our portfolio is a result of our recent merger with HBT Labs, Inc. and supports our expansion into the oncology market. We are pleased to be able to provide patients with this potentially life-extending medication, which is another product that we can proudly say has been manufactured in America," stated Joann Gioia, Vice President and Chief Commercial Officer at American Regent, Inc.

Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is a microtubule inhibitor indicated for the treatment of:

- **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
- **Non-Small Cell Lung Cancer** as first-line treatment of locally advanced or metastatic non–small cell lung cancer 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

Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is available for immediate shipment. Customers can order the product through their wholesaler/distributor, or by contacting our Customer Support Group at 1-800-645-1706.

Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is supplied as follows:

Pack NDC#	Strength	Supplied as	Shelf pack
0517-4300-01	100 mg/vial	Single-dose vial	1

Please see the Important Safety Information, including Boxed Warning, below. To view the Full Prescribing Information, please click here. For additional information on Paclitaxel, please visit www.americanregent.com.

PP-PT-US-0003

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Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)

For Intravenous Use

INDICATIONS AND USAGE

Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is a microtubule inhibitor indicated for the treatment of:

- 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, in combination with gemcitabine.

IMPORTANT SAFETY INFORMATION INCLUDING BOXED WARNING

WARNING: SEVERE MYELOSUPPRESSION

- **Do not administer Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) therapy to patients who have baseline neutrophil counts of less than 1,500 cells/mm^3**.
- **Monitor for neutropenia, which may be severe and result in infection or sepsis**.
- **Perform frequent complete blood cell counts on all patients receiving Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)**.

CONTRAINDICATIONS

- Baseline neutrophil counts of <1500 cells/mm^3.
- A history of severe hypersensitivity reactions to Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound).

WARNINGS AND PRECAUTIONS

Severe Myelosuppression

- Severe myelosuppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of protein-bound paclitaxel. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC), 47% of patients with non–small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer.
- Monitor for severe neutropenia and thrombocytopenia by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC) and Days 1, 8, and 15 (for NSCLC and for pancreatic cancer).
- Do not administer Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) to patients with baseline absolute neutrophil counts (ANC) of less than 1,500 cells/mm^3.
- In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) therapy, reduce the dose of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) in subsequent courses in patients with either MBC or NSCLC.
- In patients with MBC, resume treatment with every-3-week cycles of Paclitaxel Protein-Bound Particles after ANC recovers to a level >1500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3.
- In patients with NSCLC, resume treatment if recommended at permanently reduced doses for both weekly Paclitaxel Protein-Bound Particles and every-3-week carboplatin after ANC recovers to at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an ANC of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle.

- In patients with adenocarcinoma of the pancreas, withhold Paclitaxel Protein-Bound Particles and gemcitabine if the ANC is less than 500 cells/mm^3 or platelets are less than 50,000 cells/mm^3 and delay initiation of the next cycle if the ANC is less than 1500 cells/mm^3 or platelet count is less than 100,000 cells/mm^3 on Day 1 of the cycle. Resume treatment with appropriate dose reduction if recommended.

Severe Neuropathy

- Sensory neuropathy is dose- and schedule-dependent, occurs frequently and may require dose reduction or treatment interruption.
- If ≥ Grade 3 sensory neuropathy develops, withhold Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) treatment until resolution to Grade 1 or 2 for MBC or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses.

Sepsis

- Sepsis occurred in 5% of patients with or without neutropenia who received protein-bound paclitaxel in combination with gemcitabine.
- Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis.
- If a patient becomes febrile (regardless of ANC), initiate treatment with broad-spectrum antibiotics.
- For febrile neutropenia, interrupt Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) and gemcitabine until sepsis resolves, and if neutropenia, until neutrophils are at least 1500 cells/mm^3, then resume treatment at reduced dose levels.

Pneumonitis

- Pneumonitis, including some cases that were fatal, occurred in 4% of patients with or without neutropenia with the use of protein-bound paclitaxel in combination with gemcitabine.
- Monitor patients for signs and symptoms and interrupt Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) and gemcitabine during evaluation of suspected pneumonitis.
- Permanently discontinue treatment with Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) and gemcitabine upon making a diagnosis of pneumonitis.

Severe Hypersensitivity

- Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions. Cross-hypersensitivity between protein-bound paclitaxel and other taxane products has been reported and may include severe reactions such as anaphylaxis. Closely monitor patients with a previous history of hypersensitivity to other taxanes during initiation of therapy.
- Do not rechallenge patients who experience a severe hypersensitivity reaction to Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) with this drug.

Use in Patients with Hepatic Impairment

- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment. Closely monitor patients with hepatic impairment for severe myelosuppression. Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is not recommended in patients who have a total bilirubin >5 x ULN or AST >10 x ULN.
- For MBC and NSCLC, the starting dose should be reduced for patients with moderate or severe hepatic impairment.
- For pancreatic adenocarcinoma, Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is not recommended for patients with moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and AST ≤10 x ULN).

Albumin (Human)

- Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) contains albumin derived from human blood, which has a remote risk of viral transmission.

Embryo-Fetal Toxicity

- Can cause fetal harm when administered to a pregnant woman. (See Special Populations).
- Advise females of reproductive potential of the potential risk to a fetus.
- Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) and for at least six months after the last dose of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound).
- Advise male patients with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) and for at least three months after the last dose of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound).

ADVERSE REACTIONS

Randomized Metastatic Breast Cancer (MBC) Study

- The most common adverse reactions (≥20%) with single-agent use of Paclitaxel Protein-Bound Particles (Albumin-Bound) vs paclitaxel injection in the MBC study are alopecia (90%, 94%), neutropenia (all cases 80%, 82%; severe 9%, 22%), sensory neuropathy (any symptoms 71%, 56%; severe 10%, 2%), abnormal ECG (all patients 60%, 52%; patients with normal baseline 35%, 30%), fatigue/asthenia (any 47%, 39%; severe 8%, 3%), myalgia/arthralgia (any 44%, 49%; severe 8%, 4%), AST elevation (any 39%, 32%), alkaline phosphatase elevation (any 36%, 31%), anemia (any 33%, 25%; severe 1%, <1%), nausea (any 30%, 22%; severe 3%, <1%), diarrhea (any 27%, 15%; severe <1%, 1%), and infections (24%, 20%), respectively.
- Sensory neuropathy was the cause of discontinuation in 7/229 patients.
- Other adverse reactions of note with the use of Protein-Bound Paclitaxel vs paclitaxel injection included vomiting, fluid retention, mucositis, hypersensitivity reactions, thrombocytopenia, neutropenic sepsis, and injection site reactions. Dehydration and pyrexia were also reported.
- Overall 11% of patients experienced creatinine elevation, 1% severe.
- Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with Protein-Bound Paclitaxel and 1% were severe.
- Severe cardiovascular events possibly related to single-agent protein-bound paclitaxel occurred in approximately 3% of patients and included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension.
- Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported.

Non–Small Cell Lung Cancer (NSCLC) Study

- The most common adverse reactions (≥20%) of protein-bound paclitaxel in combination with carboplatin are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue.
- The most common serious adverse reactions of protein-bound paclitaxel in combination with carboplatin for NSCLC are anemia (4%) and pneumonia (3%).
- The most common adverse reactions resulting in permanent discontinuation of protein-bound paclitaxel are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%).
- The most common adverse reactions resulting in dose reduction of protein-bound paclitaxel are neutropenia (24%), thrombocytopenia (13%), and anemia (6%).
- The most common adverse reactions leading to withholding or delay in protein-bound paclitaxel dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%).
- The following common (≥10% incidence) adverse reactions were observed at a similar incidence in protein-bound paclitaxel plus carboplatin–treated and paclitaxel injection plus carboplatin–treated patients: alopecia (56%), nausea (27%), fatigue (25%), decreased appetite (17%), asthenia (16%), constipation (16%),

diarrhea (15%), vomiting (12%), dyspnea (12%), and rash (10%); incidence rates are for the protein bound paclitaxel plus carboplatin treatment group.

- Adverse reactions with a difference of ≥2%, Grade 3 or higher, with combination use of protein-bound paclitaxel and carboplatin vs combination use of paclitaxel injection and carboplatin in NSCLC are anemia (28%, 7%), neutropenia (47%, 58%), thrombocytopenia (18%, 9%), and peripheral neuropathy (3%, 12%), respectively.
- Adverse reactions with a difference of ≥5%, Grades 1-4, with combination use of protein-bound paclitaxel and carboplatin vs combination use of paclitaxel injection and carboplatin in NSCLC are anemia (98%, 91%), thrombocytopenia (68%, 55%), peripheral neuropathy (48%, 64%), edema peripheral (10%, 4%), epistaxis (7%, 2%), arthralgia (13%, 25%), and myalgia (10%, 19%), respectively.
- Neutropenia (all grades) was reported in 85% of patients who received protein-bound paclitaxel and carboplatin vs 83% of patients who received paclitaxel injection and carboplatin.

Pancreatic Adenocarcinoma Study

- Among the most common (≥20%) adverse reactions in the phase III study, those with a ≥5% higher incidence in the protein-bound paclitaxel/gemcitabine group compared with the gemcitabine group are neutropenia (73%, 58%), fatigue (59%, 46%), peripheral neuropathy (54%, 13%), nausea (54%, 48%), alopecia (50%, 5%), peripheral edema (46%, 30%), diarrhea (44%, 24%), pyrexia (41%, 28%), vomiting (36%, 28%), decreased appetite (36%, 26%), rash (30%, 11%), and dehydration (21%, 11%).
- Of these most common adverse reactions, those with a ≥2% higher incidence of Grade 3-4 toxicity in the protein-bound paclitaxel/gemcitabine group compared with the gemcitabine group, respectively, are neutropenia (38%, 27%), fatigue (18%, 9%), peripheral neuropathy (17%, 1%), thrombocytopenia (13%, 9%), asthenia (7%, 4%) dehydration (7%, 2%), nausea (6%, 3%), diarrhea (6%, 1%), pyrexia (3%, 1%), vomiting (6%, 4%), decreased appetite (5%, 2%), and hypokalemia (4%, 1%).
- Thrombocytopenia (all grades) was reported in 74% of patients in the protein-bound paclitaxel/ gemcitabine group vs 70% of patients in the gemcitabine group.
- The most common serious adverse reactions of protein-bound paclitaxel (with a ≥1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%), and vomiting (4%).
- The most common adverse reactions resulting in permanent discontinuation of protein-bound paclitaxel were peripheral neuropathy (8%), fatigue (4%), and thrombocytopenia (2%.)
- The most common adverse reactions resulting in dose reduction of protein-bound paclitaxel are neutropenia (10%) and peripheral neuropathy (6%).
- The most common adverse reactions leading to withholding or delay in protein-bound paclitaxel dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%), and diarrhea (5%).
- Other selected adverse reactions with a ≥5% higher incidence for all-grade toxicity in the protein-bound paclitaxel/gemcitabine group compared to the gemcitabine group, respectively, are asthenia (19%, 13%), mucositis (10%, 4%), dysgeusia (16%, 8%), headache (14%, 9%), hypokalemia (12%, 7%), cough (17%, 7%), epistaxis (15%, 3%), urinary tract infection (11%, 5%), pain in extremity (11%, 6%), arthralgia (11%, 3%), myalgia (10%, 4%), and depression (12%, 6%).

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of protein-bound paclitaxel or with paclitaxel injection and may be expected to occur with protein-bound paclitaxel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Hypersensitivity Reactions:* Severe and sometimes fatal hypersensitivity reactions. Cross-hypersensitivity between protein bound and other taxanes has been reported.
- *Cardiovascula*r: Congestive heart failure, left ventricular dysfunction, and atrioventricular block.
- *Respiratory*: Pneumonitis, interstitial pneumonia, pulmonary embolism, radiation pneumonitis, lung fibrosis.
- *Neurologic:* Cranial nerve palsies, vocal cord paresis, autonomic neuropathy resulting in paralytic ileus.

- *Vision Disorders:* Reduced visual acuity due to cystoid macular edema. Abnormal visual evoked potentials suggest persistent optic nerve damage.
- *Hepatic:* Hepatic necrosis and hepatic encephalopathy leading to death.
- *Gastrointestinal:* Intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, neutropenic enterocolitis.
- *Injection Site Reaction:* Extravasation. Severe events such as phlebitis, cellulitis, induration, necrosis, and fibrosis. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site.
- *Metabolic and Nutritional Disorders:* Tumor lysis syndrome.
- *Other Clinical Events:* Skin reactions including generalized or maculopapular rash, erythema, and pruritus. Photosensitivity reactions, radiation recall phenomenon, scleroderma, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Stevens-Johnson syndrome and toxic epidermal necrolysis. Conjunctivitis, cellulitis, and increased lacrimation.
- *Accidental Exposure*: Upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea. Following topical exposure, tingling, burning, and redness.

DRUG INTERACTIONS

- Caution should be exercised when administering Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

USE IN SPECIFIC POPULATIONS

Pregnancy

- Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) can cause fetal harm when administered to a pregnant woman. Advise females of the potential risk to a fetus and to avoid becoming pregnant while receiving protein-bound paclitaxel.

Lactation

- Nursing must be discontinued when receiving treatment with Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) and for two weeks after the last dose.

Females and Males of Reproductive Potential:

- Based on animal studies and mechanism of action, Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) can cause fetal harm when administered to a pregnant woman.
- Verify the pregnancy status of females of reproductive potential prior to starting treatment.
- Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with and for at least six months after the last dose of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound).
- Advise males with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) and for at least three months after the last dose.
- Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) may impair fertility in females and males of reproductive potential.

Pediatric

- The safety and effectiveness in pediatric patients have not been established.

Geriatric

- A higher incidence of epistaxis, diarrhea, dehydration, fatigue, and peripheral edema was found in patients 65 years or older who received protein-bound paclitaxel for MBC in a pooled analysis of clinical studies.
- Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients ≥65 years of age treated with protein-bound paclitaxel and carboplatin in NSCLC.

- Diarrhea, decreased appetite, dehydration, and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old who received protein-bound paclitaxel and gemcitabine in adenocarcinoma of the pancreas.

Renal Impairment

- There are insufficient data to permit dosage recommendations in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 mL/min).

Hepatic Impairment

- Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is not recommended for use in patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment.

OVERDOSAGE

There is no known antidote for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

DOSAGE AND ADMINISTRATION

- **DO NOT SUBSTITUTE FOR OR WITH OTHER NON-PROTEIN BOUND PACLITAXEL FORMULATIONS.** Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) has different dosage and administration instructions from other paclitaxel products.
- Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicity.
- Closely monitor the infusion site for extravasation or drug infiltration during administration.

Refer to full Prescribing Information for complete Dosage and Administration information.

For additional Important Safety Information, including BOXED WARNING, please see Full Prescribing Information.

REF-2268 7/2022

To report adverse drug events (ADEs),
product quality complaints (PQCs), or to request medical information, please call:
T 1.888.532.7998

ADEs may also be reported to the FDA:
1.800.FDA.1088
or www.fda.gov/medwatch

About American Regent

American Regent, Inc.®, a Daiichi Sankyo Group company, is an industry-leading injectable manufacturer. For over 50 years, American Regent has been developing, manufacturing, and supplying quality generic and branded injectables for healthcare providers. For more than 20 years, we have been a leader in IV iron therapy.

American Regent is committed to US-based manufacturing. To that end, over the last several years we have made significant investments in expanding and modernizing our manufacturing facilities in Ohio and New York. This expansion will nearly double our capacity and allow us to better serve our customers now and in the future.

Speed counts. Flexibility matters. Reliability and quality are paramount. Because patients should never have to wait for the medications they need.

For more information, please visit www.americanregent.com

About Daiichi Sankyo

Daiichi Sankyo is dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose "to contribute to the enrichment of quality of life around the world." In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation to realize our 2030 Vision to become an "Innovative Global Healthcare Company Contributing to the Sustainable Development of Society." For more information, please visit www.daiichisankyo.com