Doxorubicin HCl Liposome Injection (Doxil®)  
**Manufacturer:** Tibotec Therapeutics, Division of Ortho Biotech Products, LP, Johnson & Johnson  
**Updated Approval:** The U.S. Food and Drug Administration (FDA) has granted full approval to doxorubicin HCl liposome injection for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.

Originally, under the accelerated approval, this product was indicated for the treatment of patients with metastatic ovarian cancer that had not responded to chemotherapy regimens comprising paclitaxel (e.g., Taxol®, Bristol-Myers Squibb) and platinum (e.g., Platinol® [cisplatin], Bristol-Myers Squibb). This approval was based on tumor response rates from three phase 2 studies. According to the terms of the approval, Johnson & Johnson’s pharmaceutical research and development arm completed a randomized phase 3 clinical study to demonstrate the drug’s clinical benefit in patients with relapsed ovarian cancer.

The study showed that there was no significant difference in time to median disease progression \( (P = .67) \) between doxorubicin HCl liposome injection (4.1 months) and topotecan HCl (Hycamtin®, GlaxoSmithKline) (4.2 months) in patients with epithelial ovarian cancer. Thus, the label has been updated to include survival, time to disease progression, and tumor response rate.

**Description:** Doxorubicin is a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius* var. caesius. Doxorubicin HCl is the established name for \((8S,10S)\)-10-\[(3-amino-2,3,6-tri-deoxy-a-L-lyxo-hexopyranosyl)oxy\]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-7-methoxy-5,12-naphthacenedione HCl.

Doxil® is provided as a sterile, translucent, red liposomal dispersion in 10-ml single-use glass vials. Each vial contains 20 mg of doxorubicin HCl at a concentration of 2 mg/ml and a pH of 6.5. The STEALTH® liposome carriers are composed of \(N\)-(carbonyl-methoxypolyethylene glycol 2000)-1,2-di-stearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/ml; fully hydrogenated soy phosphatidyl choline (HSPC), 9.58 mg/ml; and cholesterol, 3.19 mg/ml. Each milliliter also contains ammonium sulfate,
Pharmaceutical-Approval Update: Oncology

approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. More than 90% of the drug is encapsulated in the liposomes.

**Indications:** Doxorubicin HCl liposome injection is indicated for the treatment of:

- metastatic carcinoma of the ovary in patients with disease that is refractory to paclitaxel and platinum. Refractory is defined as disease that has progressed while the patient was receiving treatment or within six months of the patient’s completing treatment.
- acquired immunodeficiency-related Kaposi’s sarcoma in patients with disease that has progressed with previous combination chemotherapy or in patients who are intolerant to such therapy.

**Pharmacology:** The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs is thought to be related to nucleotide base intercalation and to the agent's cell membrane lipid-binding activities. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin’s cytotoxic activity.

Doxorubicin’s cellular membrane-binding activity may affect several cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases, and dehydrogenases generates highly reactive species, including the hydroxyl free radical OH •. Formation of free radicals has been implicated in doxorubicin cardiotoxicity by means of copper (Cu II) and iron (Fe III) reduction at the cellular level. Cells treated with doxorubicin manifest the characteristic morphological changes associated with apoptosis (programmed cell death). Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

**Boxed Warning:** Experience with doxorubicin liposome injection at high cumulative doses is too limited to have established its effects on the myocardium. Therefore, it should be assumed that the injection has myocardial toxicity similar to that of conventional formulations of doxorubicin HCl.

Doxorubicin should be not administered to patients with a history of cardiovascular disease unless the benefits outweigh the risks. Acute infusion-related reactions have occurred in up to 10% of patients treated with doxorubicin. Serious and sometimes life-threatening or fatal allergic or anaphylactoid infusion reactions have been reported. Medications and emergency equipment to treat such reactions should be available for immediate use.

Severe myelosuppression may occur. The dosage should be reduced in patients with impaired hepatic function. Accidental substitution of doxorubicin liposome injection for doxorubicin HCl has resulted in severe side effects. Thus, no substitutions should be made.

The use of doxorubicin liposome injection should be limited to physicians experienced in the use of cancer chemotherapeutic agents.

Caution should be observed in patients who have received other anthracyclines, and the total dose of doxorubicin HCl should take into account any previous or concomitant therapy with other anthracyclines or related compounds.

Congestive heart failure or cardiomyopathy may arise after discontinuation of therapy. Patients with a history of cardiovascular disease should receive doxorubicin liposome injection only when the potential benefits of treatment outweigh the risks. Cardiac function should be carefully monitored.

The most definitive test for anthracycline myocardial injury is the endomyocardial biopsy. Other methods, such as echocardiography and gated radionuclide scans, have been used to monitor cardiac function during anthracycline therapy. Any of these methods should be used to monitor potential cardiac toxicity during doxorubicin liposome injection therapy. If these test results indicate possible cardiac injury associated with this treatment, the benefits of continued therapy must be carefully weighed against the risks of myocardial injury.

In patients with ovarian cancer, myelosuppression was generally moderate and reversible. Anemia was the most common hematological adverse drug event (ADE) (52.6%), followed by leukopenia (a white blood cell [WBC] count below 4,000 mm³, 42.2%), thrombocytopenia (24.2%), and neutropenia (an absolute neutrophil cell [ANC] count below 1,000 mm³) (19.0%).

In all patients, because of the potential for bone marrow suppression, careful hematological monitoring is required during the use of doxorubicin liposome injection. Monitoring should include WBC, ANC, and platelet counts as well as hemoglobin and hematocrit levels. With the recommended dosage schedule, leukopenia is usually transient. Patients with hematological toxicity may require a smaller dose or a delay or suspension of the injections. Persistent, severe myelosuppression may result in superinfection, neutropenic fever, or hemorrhage. Development of sepsis in the setting of neutropenia has resulted in discontinuation of treatment and, in rare cases, death.

Doxorubicin HCl liposome injection may potentiate the toxicity of other anticancer therapies. In particular, hematological toxicity is sometimes more severe when the injections are given in combination with other agents that cause bone marrow suppression.

Up to 10% of treated patients experience acute infusion-related reactions, characterized by flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, or hypotension. In most patients, these reactions resolve over the course of several hours to a day after the infusion is terminated. In some patients, the reactions resolve when the rate of infusion is slowed.

Serious and sometimes life-threatening or fatal allergic or anaphylactoid infusion reactions have been reported. Emergency equipment and medications to treat any reactions should be available for immediate use.

Most infusion-related events occurred during the first infusion. Similar reactions have not been reported with conventional doxorubicin; these presumably represent a reaction to the liposomes or one of the surface components.

Among ovarian cancer patients, 37.4% experienced palmar–
plantar erythrodysesthesia (PPE). These cutaneous eruptions are characterized by swelling, pain, erythema, and sometimes desquamation of the skin on the hands and feet, with 16.4% of the patients reporting grade 3 or 4 events. Thirteen patients (3.5%) discontinued treatment because of PPE or other skin toxicity.

**Conclusion:** The new approval of doxorubicin HCl liposome injection makes it available to patients whose ovarian cancer has progressed and has stopped responding to other chemotherapy. A phase 3 comparison clinical trial showed that the injection was as effective as a similar chemotherapy.


**Paclitaxel Protein-Bound Particles for Injectable Suspension (Abraxane™)**

**Manufacturer:** American Pharmaceutical Partners, Inc./American Bioscience, Inc.

**Description:** Abraxane™ combines the active drug paclitaxel (Taxol®, Bristol-Myers Squibb) with a natural protein (albumin) into a nanoparticle that is one-hundredth the size of a red blood cell. As a result, no solvent is needed. This product is the first approved solvent-free, nanoparticle albumin-bound chemotherapeutic agent. It has the potential to exploit an inherent pathway for albumin receptor-mediated transport of drugs across the endothelial cell walls of the tumor neovascularure.

**Indication:** Abraxane™ is indicated for the treatment of metastatic breast cancer after failure of combination chemotherapy or relapse within six months of adjuvant chemotherapy. Unless it has been clinically contraindicated, prior therapy should have included an anthracycline.

**Pharmacology:** The FDA’s approval was based on the results of clinical trials comparing the effect of albumin-bound paclitaxel particles (260 mg/m²) infused over 30 minutes with that of paclitaxel (175 mg/m²) plus standard premedication, infused over three hours. Treatment with the higher-dose, albumin-bound paclitaxel was associated with a significant increase in target lesion response rates compared with paclitaxel. In a pivotal clinical trial involving 460 women, tumors shrank in 21.5% of patients who received paclitaxel protein-bound particles for injectable suspension, compared with 11.1% of those who received paclitaxel. The manufacturer has not yet provided data on whether the suspension extended the lives of those women, which is a more important measurement.

**Precautions**

**Drug Interactions**

- The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of clinical drug interaction studies, caution should be exercised when the product is given concomitantly with known substrates of CYP2C8 and CYP3A4.
- The potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors have not been evaluated in clinical trials.
- When administered as sequential infusions, taxane derivatives should be given before platinum derivatives to limit myelosuppression and to enhance efficacy.
- CYP2C8/9 inducers may decrease the levels or effects of paclitaxel. Examples include carbamazepine, phenobarbital, phenytoin, rifampin, rifapentine, and seco Barberal.
- CYP2C8 and CYP2C9 inhibitors may increase the levels or effects of paclitaxel. Examples include delavirdine, fluconazole, gemfibrozil, ketoconazole, nicardipine, non-steroidal anti-inflammatory drugs (NSAIDs), pioglitazone, and sulfonylurides.
- CYP3A4 inducers may decrease the levels of paclitaxel. Examples include aminoglutethimide, carbamazepine, naftin, nevirapine, phenobarbital, phenytoin, and the rifamycins (e.g., rifabutin, rifampin, rifampacine, rifapentine).
- CYP3A4 inhibitors may increase the levels or effects of paclitaxel. Examples include azole antifungal agents, cipiroxacin, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, neofazodone, nicardipine, proprof, protease inhibitors, quinidine, and vergamut.
- Doxorubicin: Paclitaxel may increase doxorubicin concentrations and toxicity.

**Food Interactions:** The following herbs and nutraceuticals should be avoided with protein-bound paclitaxel: black cohosh, dong quai in patients with estrogen-dependent tumors; valerian, St. John’s wort, kava kava, and gotu kola, which may increase central nervous system depression.

**Hematology:** Protein-bound paclitaxel should not be administered to patients with baseline ANC counts of less than 1,200 cells/mm³. Frequent peripheral blood cell counts should be performed for all patients receiving this agent.

For myelotoxicity to be monitored, patients should not be re-treated with subsequent cycles of this agent until the ANC count recovers to a concentration of more than 1,500 cells/mm³ and patients have more than 100,000 cells/mm³. In the case of severe neutropenia (below 500 cells/mm³) for seven days or more during a course of Abraxane™ therapy, a dose reduction for subsequent courses of therapy is recommended.

**Nervous System:** Sensory neuropathy occurs frequently with Abraxane™. The occurrence of grade 1 or 2 sensory neuropathy does not generally warrant a dose modification. If grade 3 sensory neuropathy develops, treatment should be
withheld until there is resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of this agent.

**Conclusion:** Abraxane™ is a second-generation taxane formulation in which paclitaxel is albumin-bound and therefore water-soluble. Conversely, because paclitaxel is not miscible with water, the agent must be administered in a cremophor/alcohol–based solution, which is where most of its toxicities and dose limitation arise.

Protein-bound paclitaxel is associated with significantly less toxicity so that its formulation allows a greater dose of paclitaxel to be delivered. Patients who receive paclitaxel need premedication with steroids and antihistamines to avoid severe hypersensitivity reactions; this requirement is eliminated with the protein-bound paclitaxel. The protein-bound form can be given over 30 minutes instead of three hours.


**Erlotinib (Tarceva®)**

**Manufacturer:** Genentech, OSI Pharmaceuticals

**Description:** Erlotinib, a tyrosine kinase inhibitor, belongs to a group of cancer drugs known as epidermal growth factor receptor (EGFR)–inhibitors. EGFR-inhibitors can destroy some types of cancer cells while causing little harm to normal cells. EGFRs are proteins in the body that help to activate intracellular tyrosine kinase (an enzyme). This activity results in a cascade of intracellular signaling events, leading to cell proliferation, differentiation, cell survival, angiogenesis, and invasion or metastases. These receptors are overexpressed in numerous tumor types, and this overexpression has correlated with more aggressive tumor activity and poor clinical outcomes.

**Indication:** Erlotinib is intended for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after unsuccessful results from at least one prior chemotherapy regimen.

**Pharmacology:** Structures called EGFRs sit on the surface of many types of cancer cells. The receptors allow epidermal growth factor (EGF) to attach to them. When growth factors (such as transforming growth factor-alpha and EGF) bind to the receptors, tyrosine kinase inside the cell triggers chemical signals to make the cell grow and divide. Erlotinib attaches itself to the tyrosine kinase enzyme and prevents the receptor from being activated. This action appears to stop the cell from dividing. Erlotinib thus seems to stop cancer cells from growing.

**Boxed Warning:** There have been infrequent reports of serious interstitial lung disease (ILD), including fatalities, in patients receiving erlotinib to treat NSCLC or other advanced solid tumors. In a randomized single-agent study, the incidence of ILD (0.8%) was the same in both the placebo and erlotinib patient groups. The overall incidence in erlotinib-treated patients from all studies (including uncontrolled trials and those using concurrent chemotherapy) was approximately 0.6%.

Reported diagnoses in patients thought to have ILD included pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, and lung infiltration. Symptoms started from five days to more than nine months (median, 47 days) after erlotinib therapy was initiated. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, previous radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In the event of the acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, erlotinib therapy should be interrupted pending a diagnostic evaluation. If a diagnosis of ILD is confirmed, erlotinib should be discontinued and appropriate treatment instituted as necessary.

**Precautions:** Co-treatment with the potent CYP3A4 inhibitor ketoconazole increases the area-under-the-curve (AUC) concentration of erlotinib by two thirds. Caution should be used with coadministration of ketoconazole and other strong CYP3A4 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole). Pre-treatment with the CYP3A4 inducer rifampicin decreases the AUC of erlotinib by approximately two thirds.

Alternative treatments that lack CYP3A4-inducing activity should be considered. If an alternative treatment is unavailable, an erlotinib dose greater than 150 mg should be considered. If the erlotinib dose is adjusted upward, the dose will need to be reduced upon discontinuation of rifampicin or other CYP3A4 inducers. Other CYP3A4 inducers include rifabutin, rifapentin, phenytoin, carbamazepine, phenobarbital, and St. John’s wort.

Asymptomatic increases in liver transaminase levels have been observed in erlotinib-treated patients; therefore, periodic liver function testing of transaminases, bilirubin, and alkaline phosphatase should be considered. Reducing or interrupting the dose of erlotinib may be warranted if changes in liver function are significant.

**Conclusion:** NSCLC accounts for about 80% of all lung cancers. It is an aggressive disease, and the overall five-year survival rates are less than 10%. In a randomized, placebo-controlled trial, erlotinib improved symptoms and increased survival in patients with advanced NSCLC. The drug extended the lives of patients and improved quality of life by suppressing symptoms.