



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use doxorubicin hydrochloride safely and effectively. See full prescribing information for doxorubicin hydrochloride liposome injection.

Doxorubicin Hydrochloride Liposome Injection for intravenous infusion

Initial U.S. Approval: 1995

WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, SUBSTITUTION

See full prescribing information for complete boxed warning.

- Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin hydrochloride approaches 550 mg/m². Cardiac toxicity may also occur at lower cumulative doses with mediastinal irradiation or concurrent cardiotoxic agents (5.1).
- Acute infusion-related reactions, sometimes reversible upon terminating or slowing infusion, occurred in up to 10% of patients. Serious and sometimes fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications/emergency equipment to treat such reactions should be available for immediate use (5.2).
- Severe myelosuppression may occur (5.3).
- Reduce dosage in patients with impaired hepatic function (2.6).
- Accidental substitution of doxorubicin hydrochloride liposome injection resulted in severe side effects. Do not substitute on mg per mg basis with doxorubicin hydrochloride (2.1).

RECENT MAJOR CHANGES

Contraindications, Nursing Mother (4) Removed 9/2012

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FULL PRESCRIBING INFORMATION

WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, ACCIDENTAL SUBSTITUTION

- The use of doxorubicin hydrochloride liposome injection may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin hydrochloride approaches 550 mg/m². In a clinical study in patients with advanced breast cancer, 250 patients received doxorubicin hydrochloride liposome injection at a starting dose of 50 mg/m² every 4 weeks. At all cumulative anthracycline doses between 450 to 500 mg/m² or between 500 to 550 mg/m², the risk of cardiac toxicity for patients treated with doxorubicin hydrochloride liposome injection was 11%. Prior use of other anthracyclines or antineoplastic agents should be included in the cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy [see Warnings and Precautions (5.1)].
- Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with doxorubicin hydrochloride liposome injection. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Doxorubicin hydrochloride liposome injection should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions [see Warnings and Precautions (5.2)].
- Severe myelosuppression may occur [see Warnings and Precautions (5.3)].
- Dosage should be reduced in patients with impaired hepatic function [see Dosage and Administration (2.6) and Use in Specific Populations (8.6)].
- Accidental substitution of doxorubicin hydrochloride liposome injection for doxorubicin hydrochloride has resulted in severe side effects. Doxorubicin hydrochloride liposome injection should not be substituted for doxorubicin hydrochloride on a mg per mg basis [see Dosage and Administration (2.1)].

1 INDICATIONS AND USAGE

1.1 Ovarian Cancer

Doxorubicin hydrochloride liposome injection is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.

1.2 AIDS-Related Kaposi's Sarcoma

Doxorubicin hydrochloride liposome injection is indicated for the treatment of AIDS-related Kaposi's sarcoma in patients after failure of prior systemic chemotherapy or intolerance to such therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Usage and Administration Precautions

Liposomal encapsulation can substantially affect a drug's functional properties relative to those of the unencapsulated drug. Therefore DO NOT SUBSTITUTE one drug for the other.

Do not administer as a bolus injection or an undiluted solution. Rapid infusion may increase the risk of infusion-related reactions [see Warnings and Precautions (5.2)]. Doxorubicin hydrochloride liposome injection must not be given by the intramuscular or subcutaneous route.

Until specific compatibility data are available, it is not recommended that doxorubicin hydrochloride liposome injection be mixed with other drugs.

Doxorubicin hydrochloride liposome injection should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of doxorubicin hydrochloride liposome injection, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction.

2.2 Patients With Ovarian Cancer

Doxorubicin hydrochloride liposome injection should be administered intravenously at a dose of 50 mg/m² (doxorubicin hydrochloride equivalent) at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related adverse reactions are observed, the rate of infusion can be increased to complete administration of the drug over one hour. The patient should be dosed once every 4 weeks, for as long as the patient does not progress, shows no evidence of cardiotoxicity [see Warnings and Precautions (5.1)], and continues to tolerate treatment. A minimum of 4 courses is recommended because median time to response in clinical trials was 4 months. To manage adverse reactions such as hand-foot syndrome (HFS), stomatitis, or hematologic toxicity the doses may be delayed or reduced [see Dosage and Administration (2.5)]. Pretreatment with or concomitant use of antiemetics should be considered.

2.3 Patients With AIDS-Related Kaposi's Sarcoma

Doxorubicin hydrochloride liposome injection should be administered intravenously at a dose of 20 mg/m² (doxorubicin hydrochloride equivalent). An initial rate of 1 mg/min should be used to minimize the risk of infusion-related reactions. If no infusion-related adverse reactions are observed, the infusion rate should be increased to complete the administration of the drug over one hour. The dose should be repeated once every three weeks, for as long as patients respond satisfactorily and tolerate treatment.

2.5 Dose Modification Guidelines

Doxorubicin hydrochloride liposome injection exhibits nonlinear pharmacokinetics at 50 mg/m²; therefore, dose adjustments may result in a non-proportional greater change in plasma concentration and exposure to the drug [see Clinical Pharmacology (12.3)].

INDICATIONS AND USAGE

Doxorubicin hydrochloride is an anthracycline topoisomerase inhibitor indicated for:

- Ovarian cancer (1.1)**
After failure of platinum-based chemotherapy.
- AIDS-related Kaposi's Sarcoma (1.2)**
After failure of prior systemic chemotherapy or intolerance to such therapy.

DOSAGE AND ADMINISTRATION

Administer doxorubicin hydrochloride liposome injection at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion related reactions occur, increase rate of infusion to complete administration over 1 hour. Do not administer as bolus injection or undiluted solution (2.1).

- Ovarian cancer:** 50 mg/m² IV every 4 weeks for 4 courses minimum (2.2)
- AIDS-related Kaposi's Sarcoma:** 20 mg/m² IV every 3 weeks (2.3)

DOSAGE FORMS AND STRENGTHS

Single use vial: 20 mg/10 mL and 50 mg/25 mL (3)

CONTRAINDICATIONS

- Hypersensitivity reactions to a conventional formulation of doxorubicin hydrochloride or the components of doxorubicin hydrochloride liposome injection (4, 5.2)

WARNINGS AND PRECAUTIONS

- Hand-Foot Syndrome may occur. Dose modification or discontinuation may be required (5.4)
- Radiation recall reaction may occur (5.5)

ADVERSE REACTIONS

Most common adverse reactions (>20%) are asthenia, fatigue, fever, anorexia, nausea, vomiting, stomatitis, diarrhea, constipation, hand and foot syndrome, rash, neutropenia, thrombocytopenia and anemia (6).

To report SUSPECTED ADVERSE REACTIONS contact CARACO Pharmaceutical Laboratories Ltd. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Doxorubicin hydrochloride may interact with drugs known to interact with conventional formulations of Doxorubicin hydrochloride. (7)

USE IN SPECIFIC POPULATIONS

- Doxorubicin hydrochloride liposome injection can cause fetal harm when used during pregnancy. (5.6, 8.1)
- Discontinue nursing during treatment with doxorubicin hydrochloride liposome injection (8.3).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2012

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Patients should be carefully monitored for toxicity. Adverse reactions, such as HFS, hematologic toxicities, and stomatitis may be managed by dose delays and adjustments. Following the first appearance of a Grade 2 or higher adverse reactions, the dosing should be adjusted or delayed as described in the following tables. Once the dose has been reduced, it should not be increased at a later time.

Recommended Dose Modification Guidelines

Table 1: Hand-Foot Syndrome (HFS)

Toxicity Grade	Dose Adjustment
1 (mild erythema, swelling, or desquamation not interfering with daily activities)	Reduce unless patient has experienced previous Grade 3 or 4 HFS. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued. If resolved to Grade 0-1 within 2 weeks, and there are no prior Grade 3-4 HFS, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.
3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing).	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued.
4 (diffuse or local process causing infectious complications, or a bed ridden state or hospitalization)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued.

Table 2: Hematological Toxicity

Grade	ANC	Platelets	Modification
1	1,500 to 1,900	75,000 to 150,000	Resume treatment with no dose reduction
2	1,000 to < 1,500	50,000 to < 75,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction
3	500 to 999	25,000 to < 50,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction
4	<500	<25,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose at 25% dose reduction or continue full dose with cytokine support

Table 3: Stomatitis

Toxicity Grade	Dose Adjustment
1 (painless ulcers, erythema, or mild soreness)	Redose unless patient has experienced previous Grade 3 or 4 toxicity. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval
2 (painful erythema, edema, or ulcers, but can eat)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued. If resolved to Grade 0-1 within 2 weeks and there was no prior Grade 3-4 stomatitis, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval
3 (painful erythema, edema, or ulcers, and cannot eat)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued.
4 (requires parenteral or enteral support)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to doxorubicin hydrochloride liposome injection original dose interval. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued.

2.6 Patients With Impaired Hepatic Function

Limited clinical experience exists in treating patients with hepatic impairment with doxorubicin hydrochloride liposome injection. Based on experience with doxorubicin hydrochloride, it is recommended that the doxorubicin hydrochloride liposome injection dosage be reduced if the bilirubin is elevated as follows: serum bilirubin 1.2 to 3 mg/dL - give ½ normal dose; serum bilirubin > 3 mg/dL - give ¼ normal dose.

2.7 Preparation for Intravenous Administration

Each 10 mL vial contains 20 mg doxorubicin hydrochloride at a concentration of 2 mg/mL. Each 25 mL vial contains 50 mg doxorubicin hydrochloride at a concentration of 2 mg/mL.

Doxorubicin hydrochloride liposome injection doses up to 90 mg must be diluted in 250 mL of 5% Dextrose Injection, USP prior to administration. Doses exceeding 90 mg should be diluted in 500 mL of 5% Dextrose Injection, USP prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in doxorubicin hydrochloride liposome injection. Diluted doxorubicin hydrochloride liposome injection should be refrigerated at 2°C to 8°C (36°F to 46°F) and administered within 24 hours.

Do not use with in-line filters.

- Do not mix with other drugs.
- Do not use with any diluent other than 5% Dextrose Injection.
- Do not use any bacteriostatic agent, such as benzyl alcohol.

Doxorubicin hydrochloride liposome injection is not a clear solution but a translucent, red liposomal dispersion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

Rapid flushing of the infusion line should be avoided.

2.8 Procedure for Proper Handling and Disposal

Caution should be exercised in the handling and preparation of doxorubicin hydrochloride liposome injection.

The use of gloves is required.

If doxorubicin hydrochloride liposome injection comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

Doxorubicin hydrochloride liposome injection should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of doxorubicin hydrochloride liposome injection, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. Doxorubicin hydrochloride liposome injection must not be given by the intramuscular or subcutaneous route.

Doxorubicin hydrochloride liposome injection should be handled and disposed of in a manner consistent with other anticancer drugs. Several guidelines on this subject exist [see References (15)].

3 DOSAGE FORMS AND STRENGTHS

- Single use vial: 20 mg/10 mL
- Single use vial: 50 mg/25 mL

4 CONTRAINDICATIONS

Doxorubicin hydrochloride liposome injection is contraindicated in patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin hydrochloride or the components of doxorubicin hydrochloride liposome injection [see Warnings and Precautions (5.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Toxicity

Special attention must be given to the risk of myocardial damage from cumulative doses of doxorubicin hydrochloride. Acute left ventricular failure may occur with doxorubicin, particularly in patients who have received a total cumulative dosage of doxorubicin exceeding the currently recommended limit of 550 mg/m². Lower (400 mg/m²) doses appear to cause heart failure in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide.

Prior use of other anthracyclines or antineoplastic agents should be included in calculations of total cumulative dosage. Congestive heart failure or cardiomyopathy may be encountered after discontinuation of anthracycline therapy. Patients with a history of cardiovascular disease should be administered doxorubicin hydrochloride liposome injection only when the potential benefit of treatment outweighs the risk.

Cardiac function should be carefully monitored in patients treated with doxorubicin hydrochloride liposome injection. The most definitive test for anthracycline myocardial injury is endomyocardial biopsy. Other methods, such as echocardiography or multigated radionuclide scans, have been used to monitor cardiac function during anthracycline therapy. Any of these methods should be employed to monitor potential cardiac toxicity in patients treated with doxorubicin hydrochloride liposome injection. If these tests result indicate possible cardiac injury associated with doxorubicin hydrochloride liposome injection therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

In a clinical study in patients with advanced breast cancer, 250 patients received doxorubicin hydrochloride liposome injection at starting dose of 50 mg/m² every 4 weeks. At all cumulative anthracycline doses between 450 to 500 mg/m², or between 500 to 550 mg/m², the risk of cardiac toxicity for patients treated with doxorubicin hydrochloride liposome injection was 11%. In this study, cardiotoxicity was defined as a decrease of >20% from baseline if the resting left ventricular ejection fraction (LVEF) remained in the normal range, or a decrease of >10% if the resting LVEF became abnormal (less than the institutional lower limit of normal). The data on left ventricular ejection fraction (LVEF) defined cardiotoxicity and congestive heart failure (CHF) are in the table below.

Table 5: Number of Patients With Advanced Breast Cancer

	Doxorubicin Hydrochloride Liposome Injection (n=250)
Patients who Developed Cardiotoxicity (LVEF Defined)	10
Cardiotoxicity (With Signs & Symptoms of CHF)	0
Cardiotoxicity (no Signs & Symptoms of CHF)	10
Patients With Signs and Symptoms of CHF Only	2

5.2 Infusion Reactions

Acute infusion-related reactions were reported in 7.1% of patients treated with doxorubicin hydrochloride liposome injection in the randomized ovarian cancer study. These reactions were characterized by one or more of the following symptoms: 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, and hypotension. In most patients, these reactions resolved over the course of several hours to a day once the infusion is terminated. In some patients, the reaction resolved when the rate of infusion was slowed. In this study, two patients treated with doxorubicin hydrochloride liposome injection (0.8%) discontinued due to infusion-related reactions. In clinical studies, six patients with AIDS-related Kaposi's sarcoma (0.9%) and 13 (1.7%) solid tumor patients discontinued doxorubicin hydrochloride liposome injection therapy because of infusion-related reactions.

Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

The majority of infusion-related events occurred during the first infusion. Similar reactions have not been reported with conventional doxorubicin and they presumably represent a reaction to the doxorubicin hydrochloride liposomes or one of its surface components.

The initial rate of infusion should be 1 mg/min to help minimize the risk of infusion reactions [see Dosage and Administration (2)].

5.3 Myelosuppression

Because of the potential for bone marrow suppression, careful hematologic monitoring is required during use of doxorubicin hydrochloride liposome injection, including white blood cell, neutrophil, platelet counts, and HbA1c. With the recommended dosage schedule, leukopenia is usually transient. Hematologic toxicity may require dose reduction or delay or suspension of doxorubicin hydrochloride liposome injection therapy. 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 hydrochloride liposome injection may potentiate the toxicity of other anticancer therapies. In particular, hematologic toxicity may be more severe when doxorubicin hydrochloride liposome injection is administered in combination with other agents that cause bone marrow suppression.

In patients with relapsed ovarian cancer, myelosuppression was generally moderate and reversible. In the three single-arm studies, anemia was the most common hematologic adverse reaction (52.6%), followed by leukopenia (WBC < 4,000/mm³; 42.2%), thrombocytopenia (24.2%), and neutropenia (ANC < 1,000/mm³; 19%). In the randomized study, anemia was the most common hematologic adverse reaction (40.2%), followed by leukopenia (WBC < 4,000/mm³; 36.8%), neutropenia (ANC < 1,000/mm³; 35.1%), and thrombocytopenia (13%) [see Adverse Reactions (6.2)].

In patients with relapsed ovarian cancer, 4.6% received G-CSF (or GM-CSF) to support their blood counts [see Dosage and Administration (2.5)].

For patients with AIDS-related Kaposi's sarcoma who often present with baseline myelosuppression due to such factors as their HIV disease or concomitant medications, myelosuppression appears to be the dose-limiting adverse reaction at the recommended dose of 20 mg/m² [see Adverse Reactions (6.2)]. Leukopenia is the most common adverse reaction experienced in this population; anemia and thrombocytopenia can also be expected. Sepsis occurred in 5% of patients; for 0.7% of patients the event was considered possibly or probably related to doxorubicin hydrochloride liposome injection. Eleven patients (1.8%) discontinued study because of bone marrow suppression or neutropenia.

5.4 Hand-Foot Syndrome (HFS)

In the randomized ovarian cancer study, 50.6% of patients treated with doxorubicin hydrochloride liposome injection at 50 mg/m² every 4 weeks experienced HFS (developed palmar-plantar skin eruptions characterized by swelling, pain, erythema and, for some patients, desquamation of the skin on the hands and the feet), with 23.8% of the patients reporting HFS Grade 3 or 4 events. Ten subjects (4.2%) discontinued treatment due to HFS or other skin toxicity. HFS toxicity grades are described above [see Definitions of HFS grades in Dosage and Administration (2.5)].

Among 705 patients with AIDS-related Kaposi's sarcoma treated with doxorubicin hydrochloride liposome injection at 20 mg/m² every 2 weeks, 24 (3.4%) developed HFS, with 3 (0.9%) discontinuing.

HFS was generally observed after 2 or 3 cycles of treatment but may occur earlier. In most patients the reaction is mild and resolves in one to two weeks so that prolonged delay of therapy need not occur. However, dose modification may be required to manage HFS [see Dosage and Administration (2.5)]. The reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

5.5 Radiation Recall Reaction

Recall reaction has occurred with doxorubicin hydrochloride liposome injection administration after radiotherapy.

5.6 Fetal Mortality

Pregnancy Category D

Doxorubicin hydrochloride liposome injection can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If doxorubicin hydrochloride liposome injection is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. If pregnancy occurs in the first few months following treatment with doxorubicin hydrochloride liposome injection, the prolonged half-life of the drug must be considered. Women of childbearing potential should be advised to avoid pregnancy during treatment with doxorubicin hydrochloride liposome injection. [see Use in Specific Populations (8.1)].

5.7 Toxicity Potentialization

The doxorubicin in doxorubicin hydrochloride liposome injection may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with the conventional formulation of doxorubicin hydrochloride. Radiation-induced toxicity to the myocardium, mucosae, skin, and liver have been reported to be increased by the administration of doxorubicin hydrochloride.

5.8 Monitoring: Laboratory Tests

Complete blood counts, including platelet counts, should be obtained frequently and at a minimum prior to each dose of doxorubicin hydrochloride liposome injection [see Warnings and Precautions (5.3)].

6 ADVERSE REACTIONS

6.1 Overall Adverse Reactions Profile

The following adverse reactions are discussed in more detail in other sections of the labeling.

- Cardiac Toxicity [see Warnings and Precautions (5.1)]
- Infusion reactions [see Warnings and Precautions (5.2)]
- Myelosuppression [see Warnings and Precautions (5.3)]
- Hand-Foot syndrome [see Warnings and Precautions (5.4)]

The most common adverse reactions observed with doxorubicin hydrochloride liposome injection are asthenia, fatigue, fever, nausea, stomatitis, vomiting, diarrhea, constipation, anorexia, hand-foot syndrome, rash and neutropenia, thrombocytopenia and anemia.

patients were receiving antifungal medications, primarily fluconazole (75.8%). Seventy-two percent of patients were receiving antivirals, 56.3% acyclovir, 29% ganciclovir, and 16% foscarnet. In addition, 47.8% patients received colony-stimulating factors (sargamostim/filgrastim) sometime during their course of treatment.

Adverse reactions led to discontinuation of treatment in 5% of patients with AIDS-related Kaposi's sarcoma. Those that did so included bone marrow suppression, cardiac adverse reactions, infusion-related reactions, toxoplasmosis, HFS, pneumonia, cough/dyspnea, fatigue, optic neuritis, progression of a non-KS tumor, allergy to penicillin, and unspecified reasons.

Table 8: Hematology Data Reported in Patients With AIDS-Related Kaposi's Sarcoma

	Patients With Refractory or Intolerant AIDS-Related Kaposi's Sarcoma (n = 74)		Total Patients With AIDS-Related Kaposi's Sarcoma (n = 720)	
Neutropenia				
< 1000/mm ³	34	(45.9%)	352	(48.9%)
< 500/mm ³	8	(10.8%)	96	(13.3%)
Anemia				
< 10 g/dL	43	(58.1%)	399	(55.4%)
< 8 g/dL	12	(16.2%)	131	(18.2%)
Thrombocytopenia				
< 150,000/mm ³	45	(60.8%)	439	(60.9%)
< 25,000/mm ³	1	(1.4%)	30	(4.2%)

Table 9: Probably and Possibly Drug-Related Non-Hematologic Adverse Reactions Reported in ≥ 5% of Patients With AIDS-Related Kaposi's Sarcoma

Adverse Reactions	Patients With Refractory or Intolerant AIDS-Related Kaposi's Sarcoma (n = 77)		Total Patients With AIDS-Related Kaposi's Sarcoma (n = 705)	
Nausea	14	(18.2%)	119	(16.9%)
Asthenia	5	(6.5%)	70	(9.9%)
Fever	6	(7.8%)	64	(9.1%)
Allopia	7	(9.1%)	63	(8.9%)
Alkaline Phosphatase Increase	1	(1.3%)	55	(7.8%)
Vomiting	6	(7.8%)	55	(7.8%)
Diarrhea	4	(5.2%)	55	(7.8%)
Stomatitis	4	(5.2%)	48	(6.8%)
Oral Moniliasis	1	(1.3%)	39	(5.5%)

The following additional (not in table) adverse reactions were observed in patients with AIDS-related Kaposi's sarcoma.

Incidence 1% to 5%
Body As A Whole: headache, back pain, infection, allergic reaction, chills.

Cardiovascular: chest pain, hypotension, tachycardia.

Cutaneous: herpes simplex, rash, itching.

Digestive: mouth ulceration, anorexia, dysphagia.

Metabolic and Nutritional: SGPT increase, weight loss, hyperbilirubinemia.

Other: dyspnea, pneumonia, dizziness, somnolence.

Incidence Less Than 1%
Body As A Whole: sepsis, moniliasis, cryptococcosis.

Cardiovascular: thrombophlebitis, cardiomyopathy, palpitation, bundle branch block, congestive heart failure, heart arrest, thrombosis, ventricular arrhythmia.

Digestive: hepatitis.

Metabolic and Nutritional Disorders: dehydration

Respiratory: cough increase, pharyngitis.

Skin and Appendages: maculopapular rash, herpes zoster.

Special Senses: taste perversion, conjunctivitis.

6.3 Post Marketing Experience

The following additional adverse reactions have been identified during post approval use of doxorubicin hydrochloride liposome injection. 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.

Musculoskeletal and Connective Tissue Disorders: rare cases of muscle spasms.

Respiratory, Thoracic and Mediastinal Disorders: rare cases of pulmonary embolism (in some cases fatal).

Hematologic disorders: Secondary acute myelogenous leukemia with and without fatal outcome has been reported in patients whose treatment included doxorubicin hydrochloride liposome injection.

Skin and subcutaneous tissue disorders: rare cases of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with doxorubicin hydrochloride liposome injection. Doxorubicin hydrochloride liposome injection may interact with drugs known to interact with the conventional formulation of doxorubicin hydrochloride.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.6)].

Doxorubicin hydrochloride liposome injection is embryotoxic at doses of 1 mg/kg/day in rats and is embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about one-eighth the 50 mg/m² human dose on a mg/m² basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced live litter sizes.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs, including antineoplastic agents, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from doxorubicin hydrochloride liposome injection, discontinue nursing during treatment with doxorubicin hydrochloride liposome injection.

8.4 Pediatric Use

The safety and effectiveness of doxorubicin hydrochloride liposome injection in pediatric patients have not been established.

8.5 Geriatric Use

Of the patients treated with doxorubicin hydrochloride liposome injection in the randomized ovarian cancer study, 34.7% (n=83) were 65 years of age or older while 7.9% (n=19) were 75 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Hepatic Impairment

The pharmacokinetics of doxorubicin hydrochloride liposome injection has not been adequately evaluated in patients with hepatic impairment. Doxorubicin is eliminated in large part by the liver. Thus, doxorubicin hydrochloride dosage should be reduced in patients with impaired hepatic function [see Dosage and Administration (2.6)].

Prior to doxorubicin hydrochloride liposome injection administration, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase, and bilirubin [see Dosage and Administration (2.6)].

10 OVERDOSAGE

Acute overdosage with doxorubicin hydrochloride causes increases in mucositis, leucopenia, and thrombocytopenia.

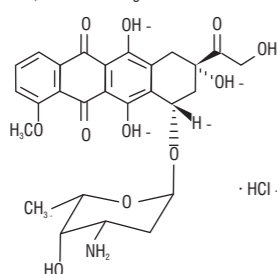
Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions, and symptomatic treatment of mucositis.

11 DESCRIPTION

Doxorubicin hydrochloride liposome injection is doxorubicin hydrochloride encapsulated in pegylated liposomes for intravenous administration.

Doxorubicin is an anthracycline topoisomerase inhibitor isolated from *Streptomyces peucetius* var. *caesius*.

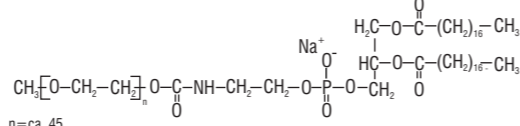
Doxorubicin hydrochloride, which is the established name for (8S,10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexaperyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthoquinone hydrochloride, has the following structure:



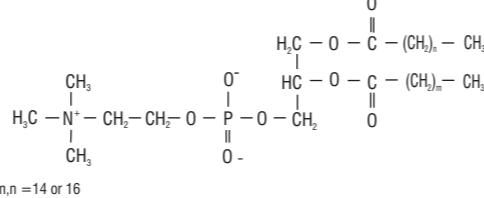
The molecular formula of the drug is C₂₇H₃₉NO₁₁·HCl; its molecular weight is 579.99.

Doxorubicin hydrochloride liposome injection is provided as a sterile, translucent, red liposomal dispersion in 10 mL or 25 mL glass, single use vials. Each vial contains 20 mg or 50 mg doxorubicin hydrochloride, USP at a concentration of 2 mg/mL and a pH of 6.5. The pegylated liposome carriers are composed of cholesterol, 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and N-(carboxymethyl)polyethylene glycol 2000-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg, histidine as a buffer, hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the pegylated liposomes.

MPEG-DSPE has the following structural formula: -



HSPC has the following structural formula: -



m, n = 14 or 16

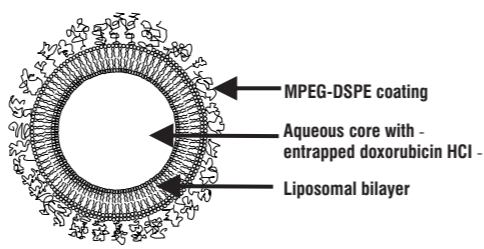
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active ingredient of doxorubicin hydrochloride liposome injection is doxorubicin hydrochloride. The mechanism of action of doxorubicin hydrochloride is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

Doxorubicin hydrochloride liposome injection is doxorubicin hydrochloride encapsulated in long-circulating pegylated liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The pegylated liposomes of doxorubicin hydrochloride liposome injection are formulated with surface-bound methoxy polyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

Representation of a pegylated liposome:



Pegylated liposomes have a half-life of approximately 55 hours in humans. They are stable in blood, and direct measurement of liposomal doxorubicin shows that at least 90% of the drug (the assay used cannot quantify less than 5 to 10% free doxorubicin) remains liposome-encapsulated during circulation.

It is hypothesized that because of their small size (ca. 100 nm) and persistence in the circulation, the pegylated doxorubicin hydrochloride liposomes are able to penetrate the altered and often compromised vasculature of tumors. This hypothesis is supported by studies using colloidal gold-containing pegylated liposomes, which can be visualized microscopically. Evidence of penetration of pegylated liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C-26 colon carcinoma tumors and in transgenic mice with Kaposi's sarcoma-like lesions. Once the pegylated liposomes distribute to the tissue compartment, the encapsulated doxorubicin hydrochloride becomes available. The exact mechanism of release is not understood.

12.3 Pharmacokinetics

The plasma pharmacokinetics of doxorubicin hydrochloride liposome injection were evaluated in 42 patients with AIDS-related Kaposi's sarcoma (KS) who received single doses of 10 or 20 mg/m² administered by a 30-minute infusion. Twenty-three of these patients received single doses of both 10 and 20 mg/m² with a 3-week wash-out period between doses. The pharmacokinetic parameter values of doxorubicin hydrochloride liposome injection, given for total doxorubicin (mostly liposomal bound), are presented in Table 11.

Table 11: Pharmacokinetic Parameters of Doxorubicin Hydrochloride Liposome Injection in Patients With AIDS-Related Kaposi's Sarcoma

Parameter (units)	Dose	
	10 mg/m ²	20 mg/m ²
Peak Plasma Concentration (mcg/mL)	4.12 ± 0.215	8.34 ± 0.49
Plasma Clearance (L/h/m ²)	0.056 ± 0.01	0.041 ± 0.004
Steady State Volume of Distribution (L/m ²)	2.83 ± 0.145	2.72 ± 0.12
AUC (mcg/mL·h)	277 ± 32.9	590 ± 58.7
First Phase (λ ₁) Half-Life (h)	4.7 ± 1.1	5.2 ± 1.4
Second Phase (λ ₂) Half-Life (h)	52.3 ± 5.6	55 ± 4.8

N = 23 -
 Mean ± Standard Error

Doxorubicin hydrochloride liposome injection displayed linear pharmacokinetics over the range of 10 to 20 mg/m². Disposition occurred in two phases after doxorubicin hydrochloride liposome injection administration, with a relatively short first phase (~5 hours) and a prolonged second phase (~55 hours) that accounted for the majority of the area under the curve (AUC).

The pharmacokinetics of doxorubicin hydrochloride liposome injection at a 50 mg/m² dose is reported to be nonlinear. At this dose, the elimination half-life of doxorubicin hydrochloride liposome injection is expected to be longer and the clearance lower compared to a 20 mg/m² dose. The exposure (AUC) is thus expected to be more than proportional at a 50 mg/m² dose when compared with the lower doses.

Distribution:

In contrast to the pharmacokinetics of doxorubicin, which displays a large volume of distribution, ranging from 700 to 1100 L/m², the small steady state volume of distribution of doxorubicin hydrochloride liposome injection shows that doxorubicin hydrochloride liposome injection is confined mostly to the vascular fluid volume. Plasma protein binding of doxorubicin hydrochloride liposome injection has not been determined; the plasma protein binding of doxorubicin is approximately 70%.

Metabolism:

Doxorubicin, the major metabolite of doxorubicin, was detected at very low levels (range: of 0.8 to 26.2 ng/mL) in the plasma of patients who received 10 or 20 mg/m² doxorubicin hydrochloride liposome injection.

Excretion:

The plasma clearance of doxorubicin hydrochloride liposome injection was slow, with a mean clearance value of 0.041 L/h/m² at a dose of 20 mg/m². This is in contrast to doxorubicin, which displays a plasma clearance value ranging from 24 to 35 L/h/m².

Because of its slower clearance, the AUC of doxorubicin hydrochloride liposome injection, primarily representing the circulation of liposome-encapsulated doxorubicin, is approximately two to three orders of magnitude larger than the AUC for a similar dose of conventional doxorubicin hydrochloride as reported in the literature. -

Special Populations:

The pharmacokinetics of doxorubicin hydrochloride liposome injection have not been separately evaluated in women, in members of different ethnic groups, or in individuals with renal or hepatic insufficiency.

Drug-Drug Interactions:

Drug-drug interactions between doxorubicin hydrochloride liposome injection and other drugs, including antiviral agents, have not been adequately evaluated in patients with ovarian cancer or AIDS-related Kaposi's sarcoma.

Tissue Distribution in Patients with Kaposi's Sarcoma:

Kaposi's sarcoma lesions and normal skin biopsies were obtained at 48 and 96 hours post infusion of 20 mg/m² doxorubicin hydrochloride liposome injection in 11 patients. The concentration of doxorubicin hydrochloride liposome injection in KS lesions was a median of 19 (range, 3 to 53) times higher than in normal skin at 48 hours post treatment; however, this was not corrected for likely differences in blood content between KS lesions and normal skin. The corrected ratio will be between 1 and 22 times. Thus, higher concentrations of doxorubicin hydrochloride liposome injection are delivered to KS lesions than to normal skin.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Although no studies have been conducted with doxorubicin hydrochloride liposome injection, doxorubicin hydrochloride and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models.

Pegylated liposomes without drug were negative when tested in Ames, mouse lymphoma and chromosomal aberration assays *in vitro*, and mammalian micronucleus assay *in vivo*.

The possible adverse effects on fertility in males and females in humans or experimental animals have not been adequately evaluated. However, doxorubicin hydrochloride liposome injection resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 mg/kg (about twice the 50 mg/m² human dose on a mg/m² basis). Decreased testicular weights and hypospermia were present in rats after repeat doses ≥ 0.25 mg/kg/day (about one third the 50 mg/m² human dose on a mg/m² basis), and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis were observed in dogs after repeat doses of 1 mg/kg/day (about one half the 50 mg/m² human dose on a mg/m² basis).

14 CLINICAL STUDIES

14.1 Ovarian Cancer

Doxorubicin hydrochloride liposome injection was studied in three open-label, single-arm, clinical studies of 176 patients with metastatic ovarian cancer. One hundred forty-five (145) of these patients were refractory to both paclitaxel- and platinum-based chemotherapy regimens.

Refractory ovarian cancer is defined as disease progression while on treatment, or relapse within 6 months of completing treatment. Patients in these studies received doxorubicin hydrochloride liposome injection at 50 mg/m² infused over one hour every 3 or 4 weeks for 3 to 6 cycles or longer in the absence of dose-limiting toxicity or progression of disease.

The baseline demographics and clinical characteristics of the patients with refractory ovarian cancer are provided in Table 12 below.

Table 12: Patient Demographics for Patients With Refractory Ovarian Cancer From Single Arm Ovarian Cancer Studies

	Study 1 (U.S.) (n = 27)	Study 2 (U.S.) (n = 82)	Study 3 (non-U.S.) (n = 36)
Age at Diagnosis (Years)			
Median	64	61.5	51.5
Range	46 to 75	34 to 85	22 to 80
Drug-Free Interval (Months)			
Median	1.8	1.7	2.6
Range	0.5 to 15.6	0.6 to 7	0.7 to 15.2
Sum of Lesions at Baseline (cm ²)			
Median	25	18.3	32.4
Range	1.2 to 230	1.3 to 285	0.3 to 114
FIGO Staging			
I	1 (3.7%)	3 (3.7%)	4 (11.1%)
II	3 (11.1%)	3 (3.7%)	1 (2.8%)
III	15 (55.6%)	60 (73.2%)	24 (66.7%)
IV	8 (29.6%)	16 (19.5%)	6 (16.7%)
Not Specified	—	—	1 (2.8%)
CA-125 at Baseline			
Median	123.5	199	1004.5
Range	20 to 14,012	7 to 46,594	20 to 12,089
Number of Prior Chemotherapy Regimens			
1	7 (25.9%)	13 (15.9%)	9 (25%)
2	11 (40.7%)	44 (53.7%)	19 (52.8%)
3	6 (22.2%)	25 (30.5%)	8 (22.8%)
4	3 (11.1%)	—	—

The primary efficacy parameter was response rate for the population of patients refractory to both paclitaxel- and a platinum-containing regimen. Assessment of response was based on Southwest Oncology Group (SWOG) criteria, and required confirmation four weeks after the initial observation. Secondary efficacy parameters were time to response, duration of response, and time to progression.

The response rates for the individual single arm studies are given in Table 13 below.

Table 13: Response Rates in Patients With Refractory Ovarian Cancer From Single Arm Ovarian Cancer Studies

	Study 1 (U.S.)	Study 2 (U.S.)	Study 3 (non-U.S.)
Response Rate	22.2% (6/27)	17.1% (14/82)	0% (0/36)
95% Confidence Interval	8.6% to 42.3%	9.7% to 27%	0% to 9.7%

When the data from the single arm studies are combined, the response rate for all patients refractory to paclitaxel and platinum agents was 13.8% (20/145) (95% CI 8.1% to 19.3%). The median time to progression was 15.9 weeks, the median time to response was 17.6 weeks, and the duration of response was 39.4 weeks.

Doxorubicin hydrochloride liposome injection was also studied in a randomized, multicenter, open-label, study in 474 patients with epithelial ovarian cancer after platinum-based chemotherapy. Patients in this study received an initial dose of either doxorubicin hydrochloride liposome injection 50 mg/m² infused over one hour every 4 weeks or topotecan 1.5 mg/m² infused daily for 5 consecutive days every 3 weeks. Patients were stratified according to platinum sensitivity and the presence of bulky disease (presence of tumor mass greater than 5 cm in size). Platinum sensitivity is defined by response to initial platinum-based therapy and a progression-free interval of greater than 6 months off treatment. The primary efficacy endpoint for this study was time to progression (TTP). Other efficacy endpoints included overall survival and objective response rate.

The baseline patient demographic and clinical characteristics are provided in Table 14 below.

Table 14: Ovarian Cancer Randomized Study Baseline Demographic and Clinical Characteristics

	Doxorubicin Hydrochloride Liposome Injection (n = 239)	Topotecan (n = 235)
Age at Diagnosis (Years)		
Median	60	60
Range	27 to 87	25 to 85
Drug-Free Interval (Months)		
Median	7	6.7
Range	0.9 to 82.1	0.5 to 109.6
FIGO Staging		
I	11 (4.6%)	15 (6.4%)
II	13 (5.4%)	8 (3.4%)
III	175 (73.2%)	164 (69.8%)
IV	40 (16.7%)	48 (20.4%)
Platinum Sensitivity		
Sensitive	109 (45.6%)	110 (46.8%)
Refractory	130 (54.4%)	125 (53.2%)
Bulky Disease		
Present	108 (45.2%)	105 (44.7%)
Absent	131 (54.8%)	130 (55.3%)

Study results are provided in Table 15.

There was no statistically significant difference in TTP between the two treatment arms.

Table 15: Results of Efficacy Analyses^a

TTP (Protocol Specified Primary Endpoint)	Protocol Defined ITT Population	
	Doxorubicin Hydrochloride Liposome Injection (n = 239)	Topotecan (n = 235)
Median (Months) ^b	4.1	4.2