Skin and subcutaneous tissue disorders: Rash (It includes rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, exfoliative rash, and rash generalized), Hand-foot syndrome.

WARNING(S)

Cardiac Toxicity

Experience with large cumulative doses of Doxorubicin HCl liposome injection is limited. The cardiac risk associated with the use of i-dox® compared to conventional Doxorubicin formulations has not been adequately evaluated, therefore warnings related

To the use of conventional formulation Doxorubicin HCl should be strictly observed. In patients receiving total Doxorubicin dosage exceeding the recommended limit of 550 mg/m^2, acute left ventricular failure may be expected to occur. Lower doses (400 mg/m^2) may cause heart failure in patients who have received mediastinal radiotherapy or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. Caution should be observed in patients who receive anthracycline therapy and the total dose of Doxorubicin HCl given should take into account for any previous or concomitant therapy with other anthracyclines or related compounds. Congestive heart failure and/or cardiomyopathy may be encountered after discontinuation of therapy. The most definitive test for anthracycline myocardial injury is endomyocardial biopsy but other methods, such as echocardiography or gated radionuclide scans may be used to monitor cardiac function during anthracycline therapy. Any of the above methods should be employed to monitor potential cardiac toxicity during i-dox® therapy. If the test results indicate possible cardiac injury associated with i-dox® therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury. AIDS related Kaposi syndrome patients may experience cardiac-related adverse events such as cardiomyopathy and/or congestive heart failure, arrhythmia (nonspecific), cardiomyopathy, heart failure, pericardial effusion, and tachycardia. Patients with a history of cardiovascular disease should be administered i-dox® only when the potential benefit of treatment outweighs the risk. Cardiac function should be carefully monitored in patients treated with i-dox®.

Myelosuppression

In ovarian cancer patients myelosuppression may be moderate and reversible; Anemia may be the most common hematologic adverse event followed by leukopenia (WBC < 4000 mm^3), thrombocytopenia and neutropenia. Some ovarian cancer patients may receive G-CSF (or GM-CSF) to support their blood counts. Myelosuppression appears to be the dose limiting adverse event in AIDS related Kaposi syndrome patients (presenting baseline myelosuppression due to factors such as HIV disease or concomitant medications) on the recommended dose of 20 mg/m^2. Leukopenia is the most common adverse event experienced in AIDS related Kaposi syndrome patients; however anemia and thrombocytopenia can also be expected. Careful hematologic monitoring is required in patients because of the potential for bone marrow suppression, during i-dox® therapy, including white blood cell, neutrophil, platelet counts, and Hgb/Hct. Leukopenia is usually transient with the recommended dosage schedule and hematologic toxicity may require dose reduction or delay or suspension of i-dox® therapy. Persistent and severe myelosuppression may result in superinfection, neutropenic fever or hemorrhage. i-dox® therapy may potentiate the toxicity of other anticancer therapies and in particular, hematologic toxicity may be augmented when i-dox® is administered in combination with other agents that cause bone marrow suppression.

Infusion related reactions

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, pruritis, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and/or hypotension occur in up to 10 % of patients on liposomal Doxorubicin HCl therapy. In most patients infusion related reactions resolve over the course of several hours to a day once the infusion is terminated and in some patients the reaction resolves when the rate of infusion is slowed. Serious and sometimes life threatening, 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. Majority of infusion related events may occur during the first infusion. Such reactions presumably may be due to a reaction to Doxorubicin HCl liposomes or one of its surface components. The initial rate of infusion should be 1 mg/min to minimize the risk of infusion reactions.

Palmar Plantar Erythrodysesthesia

PPE may be experienced in ovarian cancer patients (with skin eruptions characterized by swelling, pain, erythema and desquamation of the skin on the hands and the feet for some patients). PPE may be generally seen after 2 or 3 cycles of treatment but may occur earlier. The reaction is expected to be mild and resolve in one to two weeks so that prolonged delay of therapy need not occur. However, dose modification may be required to manage PPE. Treatment may need to be discontinued due to severe and debilitating PPE or other skin toxicity in some patients.

Pregnancy Category D

Doxorubicin HCl liposome injection can cause fetal harm when administered to pregnant women, since Doxorubicin HCl liposome injection is embryotoxic at doses of 1 mg/kg/day in rats, embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about 1/8th of the 50 mg/m^2 human dose on mg/m^2 basis). Embryotoxicity is characterized by increased embryo fetal deaths and reduced live litter sizes; however there are no adequate and well controlled studies in pregnant women. If i-dox® is to be used during pregnancy or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazards to the fetus. The prolonged half life of the drug must be considered if pregnancy occurs in the first few months following treatment with i-dox®. Women of childbearing potential should be advised to avoid pregnancy when on i-dox® therapy.

Toxicity potentiation

Doxorubicin HCl in i-dox® may potentiate the toxicity of other anticancer therapies; exacerbation of cyclophosphamide induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine has been reported for conventional Doxorubicin HCl formulation. Radiation induced toxicity of the myocardium, mucosae, skin, and liver may be increased to the as cited in reports.

Injection site effects

i-dox® is not a vesicant, but is considered to be an irritant and precautions should be taken to avoid extravasation occurring by the intravenous administration of i-dox® 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 occur, 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 help to alleviate local reaction. i-dox® should not be given by the intramuscular or subcutaneous route.

Hepatic Impairment

Doxorubicin HCl is eliminated largely by the liver, but the pharmacokinetics of i-dox® has not been adequately evaluated in patients with hepatic impairment. Thus, the dosage of i-dox® should be reduced in patients with impaired hepatic function. Prior to i-dox® administration, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Secondary acute myelogenous leukemia has been reported in patients treated with topoisomerase II inhibitors, including anthracyclines. Doxorubicin HCl and related compounds have shown mutagenic and carcinogenic properties when tested in experimental models. The possible adverse effects on fertility in males and females in humans or experimental animals have not been adequately evaluated.

PRECAUTION(S)

General

Patients on i-dox® therapy should be monitored by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are manageable with dose reductions or delays.

Laboratory Tests

Complete blood counts, including platelet counts, should be obtained frequently and at a minimum prior to each dose of i-dox®.

Drug Interactions

No formal drug interaction studies have been conducted with i-dox®, but until specific compatibility data is available, it is recommended that i-dox® should strictly not be mixed with other drugs since drugs are known to interact with the conventional Doxorubicin HCl formulation.

Pregnancy: Pregnancy Category D

Nursing mothers: No specific reports is available whether the drug is excreted in human milk but many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from mothers should be advised to discontinue nursing prior to i-dox® therapy.

Pediatric Use

The safety and effectiveness of i-dox® in pediatric patients has not been established.

Geriatric Use

No overall differences are observed between younger and older subjects, but greater sensitivity of older individuals cannot be ruled out; however there is insufficient data for a comparative evaluation of efficacy according to age.

Radiation Therapy

Skin reaction may be recalled due to i-dox® administration following radiotherapy.

Information for the Patient

Patients and patients' caregivers should be informed of the expected adverse effects of i-dox®, particularly hand foot syndrome (Palmar-Plantar Erythrodysesthesia - tingling or burning, redness, flaking, bothersome swelling, small blisters, or small sores on the palms of their hands or soles of their feet), stomatitis (painful redness, swelling, or sores in the mouth), neutropenia and its complications of neutropenic fever (100.5 °F or higher), infection, sepsis, nausea, vomiting, tiredness, weakness, rash and mild hair loss. The treating physician should be informed about these symptoms.

OVERDOSAGE(S)

Acute overdosage with Doxorubicin HCl causes increases in mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage includes hospitalization, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

Chronic overdosage with cumulative doses of doxorubicin HCl exceeding 550 mg/m^2 body surface, increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. Reduction of afterload with vasodilating agents has been recommended.

STORAGE

Store unopened vials of i-dox® at 2- 8°C (36-46°F). Do not Freeze. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on i-dox®.

PRESENTATION

i-dox® (Doxorubicin HCl liposome injection) is supplied as a sterile, translucent, red liposomal dispersion in 10 ml & 30 ml single use glass vials containing 20 mg & 50 mg of Doxorubicin HCl respectively at a concentration of 2 mg/ml. Store unopened vials of i-dox® at 2- 8°C (36-46°F). Do not Freeze.

HANDLING AND DISPOSAL

Caution should be exercised in the handling and preparation of i-dox®, the use of gloves is mandatory. If i-dox® comes into contact with skin or mucosa, wash thoroughly with soap and water. i-dox® should be considered as an irritant and precautions should be taken to avoid extravasation which may occur with or without an accompanying stinging or burning sensation. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. i-dox® must not be given by the intramuscular or subcutaneous route. i-dox® should be handled and disposed of in a manner consistent with other anticancer drugs.

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GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Doxorubicin Hydrochloride Liposome Injection
(As Pegylated Liposome)

i-dox®

FOR USE AS INTRAVENOUS INFUSION ONLY

Rx only

WARNING

Experience with i-dox® (Doxorubicin HCl liposome injection) at high cumulative doses is too limited to establish its effects on the myocardium and thus therefore be assumed that i-dox® will have myocardial toxicity similar to conventional formulations of Doxorubicin HCl. Irreversible myocardial toxicity leading to congestive heart failure often unresponsive to cardiac supportive therapy may be encountered as the total dosage of Doxorubicin HCl approaches 550 mg/m^2. Cardiac toxicity also may occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy. i-dox® should be administered to patients with a history of cardiovascular disease only if the benefit outweighs the risk to the patient.

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 may occur in patients treated with i-dox®. These reactions will resolve over the course of several hours to a day once the infusion is terminated or by slowing of the infusion rate. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported with Doxorubicin hydrochloride liposome injection. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. i-dox® should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions.

Severe myelosuppression may occur.

Dosage should be reduced in patients with impaired hepatic function.

i-dox® should not be substituted with conventional formulations of Doxorubicin HCl. on a mg per mg basis. Accidental substitution of i-dox® (Doxorubicin HCl liposome injection) with conventional formulations of Doxorubicin HCl. will result in severe side effects.

i-dox® should be administered only under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

i-dox® (Doxorubicin HCl liposome injection) is Doxorubicin hydrochloride (HCl) encapsulated in Stealth liposomes for intravenous administration.

Note: Liposomal encapsulation substantially affects a drug's functional properties relative to those of the unencapsulated drug. Different liposomal drug products may vary from one another in chemical composition and physical form of the liposomes; these differences substantially affect the functional properties of liposomal drug products. Hence do not substitute.

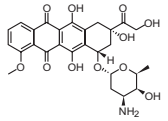
Doxorubicin is a cytotoxic anthracycline antibiotic isolated from Streptomyces peucetius var. Caesius.

i-dox® is provided as a sterile, translucent, red liposomal dispersion in 10 ml & 30 ml single use glass vials; each vial contains 20 mg & 50 mg of Doxorubicin HCl respectively at a concentration of 2 mg/ml. The stealth liposome carriers are composed of N - (carbonyl - methoxypolyethylene glycol 2000) - 1, 2 - distearoyl - sn - glycerol - 3 - phosphoethanolamine sodium salt (MPEG-DSPE), fully hydrogenated soy phosphatidylcholine (HSPC). The above process of pegylation protects liposomes from detection by mononuclear phagocyte system and to increases the blood circulation time. Greater than 90 % of the drug is encapsulated in the stealth liposomes.

i-dox® is Doxorubicin HCl encapsulated in long circulating stealth liposomes, which are microscopic vesicles composed of a phospholipid bilayer. The stealth liposomes of i-dox® are formulated with surface bound methoxypolyethylene glycol (MPEG), by a process referred to as pegylation, which protects liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time. Stealth liposomes have an approximate half-life of 55 hours in humans; they are stable in blood and direct measurement of liposomal doxorubicin shows that at least 90 % of the drug (assay procedure used cannot quantify less than 5-10 % of free Doxorubicin) remains liposome-encapsulated while in circulation. It is hypothesized that owing to the small size (ca. 100 nm) and persistence in circulation, pegylated i-dox® liposomes are able to penetrate the altered and often compromised vasculature of tumors. Once the Stealth liposomes distribute in the tissue compartment, the encapsulated Doxorubicin HCl becomes available. However the exact release mechanism is not fully understood.

CHEMICAL STRUCTURE

Doxorubicin HCl, which is the established name for (8S, 10S) - 10 - (4 - amino - 5 - hydroxyl - 6 - methyl - tetrahydro - 2H - pyran - 2 - yloxy) - 6, 8, 11 - trihydroxy - 8 - (2 - hydroxyacetyl) - 1 - methoxy - 7, 8, 9, 10 - tetrahydrotetracene - 5, 12 - dione has the following structure:



Doxorubicin HCl has a molecular formula $C_{27}H_{29}NO_{11}\cdot HCl$ and the molecular weight is 579.99.

COMPOSITION.

Each ml contains	
Doxorubicin HCl IP (as pegylated liposome)	2 mg
Water for injection IP	q.s

CLINICAL PHARMACOLOGY

Mode of Action

The precise mechanism(s) of the antineoplastic action of Doxorubicin HCl, the active ingredient of i-dox® is not fully understood, however experimental evidences indicate that Doxorubicin forms complex with DNA, by intercalation between base pairs, causing inhibition of DNA synthesis and DNA dependent RNA synthesis thus resulting in template disorder, steric obstruction and inhibition of protein synthesis. Doxorubicin is active throughout the cell cycle including interphase. Of the in-vitro cell types tested, cardiac cells are most sensitive to the effects of doxorubicin, followed by sarcoma and melanoma

cells, normal muscle fibroblasts, and normal skin fibroblasts; normal, rapidly proliferating tissues such as those of the bone marrow, gastrointestinal and oral mucosa, and hair follicles are also affected to varying degrees. Doxorubicin also has immunosuppressive activity. Cell structure studies demonstrate rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, induction of mutagenesis and chromosomal aberrations.

PHARMACOKINETICS & PHARMACODYNAMICS

Pharmacokinetics

i-dox® displays linear pharmacokinetics over the range of 10 - 20 mg/m^2. Disposition occurrs in two phases after administration of Doxorubicin HCl liposome injection, with a relatively short first phase (≈5 hours) and a prolonged second phase (≈55 hours) which accounts for majority of the area under the curve (AUC). The pharmacokinetics of Doxorubicin HCl liposome injection at a 50 mg/m^2 dose is reported to be nonlinear. At this dose, the elimination half-life of Doxorubicin HCl liposome injection is expected to be longer and the clearance is lower as compared to the 20 mg/m^2 dose. With 50 mg/m^2 dose, the exposure (AUC) is expected to be more than proportional as compared to the lower doses.

Distribution: In contrast to the large volume of distribution (Vd) of Doxorubicin (700 - 1100 L/m^2), the small steady state volume of distribution of Doxorubicin HCl liposome injection shows predominant confinement in the vascular fluid volume. The plasma protein binding of Doxorubicin is approximately 70 % while plasma protein binding of Doxorubicin HCl liposome injection has not been determined.

Metabolism: Reports indicate that Doxorubicinol, the major metabolite of Doxorubicin has been detected at very low levels (0.8 - 26.2 ng/ml) in the plasma of patients who received 10 or 20 mg/m^2 Doxorubicin HCl liposome injection.

Excretion: The mean plasma clearance value of Doxorubicin HCl liposome injection is as slow as 0.041 L/h/m^2 at a dose of 20 mg/m^2 in contrast to Doxorubicin which has a plasma clearance value ranging from 24 - 35 L/h/m^2. Owing to slower clearance, the AUC of Doxorubicin HCl liposome injection (which majorly represents the circulation of liposome encapsulated Doxorubicin) is just about larger by 2 - 3 orders of magnitude than the AUC for a similar dose of conventional Doxorubicin HCl as reported in literatures.

Special Populations: Separate evaluation of Doxorubicin HCl liposome injection pharmacokinetics has not been performed in women, individuals with renal or hepatic insufficiency and in individuals of ethnic groups.

Drug-Drug Interactions: Drug-drug interactions between Doxorubicin HCl liposome injection and other drugs, including antiviral agents have not been evaluated.

Tissue Distribution: Reports suggest that the concentration of Doxorubicin HCl liposome injection in Kaposi's sarcoma lesions and normal skin biopsies obtained at 48 and 96 hours post infusion of 20 mg/m^2, was a median of 19 (range, 3-53) times higher than in normal skin at 48 hours post treatment; however this may not have been corrected for the likely differences in blood content between KS lesions and normal skin. The corrected ratio may lie between 1 and 22 times. Thus it can be concluded that higher concentrations of Doxorubicin HCl liposome injection are delivered to KS lesions than to the normal skin.

DOSAGE AND ADMINISTRATION

Each 10 ml & 30 ml vials contains 20 mg & 50 mg of Doxorubicin HCl respectively at a concentration of 2 mg/ml.

Preparation for Intravenous Administration: A maximum dose of 90 mg diluted in 250 ml of 5 % Dextrose injection IP / USP prior to administration is the most appropriate dose of i-dox®. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is incorporated in the preparation of i-dox®. Diluted i-dox® should be refrigerated between 2-8 °C (36-46 °F) and administered within 24 hours. Diluted preparation of i-dox® for intravenous administration should not be used with in line filters nor used with any diluent other than 5 % dextrose injection and, should not be used with any bacteriostatic agent such as benzyl alcohol. i-dox® is an unclear translucent, red liposomal dispersion. i-dox® should be visually inspected for particulate matter and discoloration prior to administration and should not be used if precipitate or foreign matter is present.

It is strictly recommended that i-dox® should not be mixed with other drugs as Doxorubicin HCl liposome injection is considered to be an irritant and necessary precautions should be taken to avoid extravasation. Extravasation may occur with or without an accompanying stinging or burning sensation on intravenous administration of i-dox® even if blood returns well on aspiration of the infusion needle. Infusion should be promptly terminated if any signs or symptoms of extravasation are seen and restarted in another vein. The application of ice over the site of extravasation for around 30 minutes may be helpful to alleviate local reaction.

i-dox® should not be given by intramuscular or subcutaneous route.

In general, Doxorubicin HCl liposome injection should not be administered as a bolus injection or as an undiluted solution. Rapid infusion may attenuate the risk of infusion-related reactions.

In ovarian cancer patients, Doxorubicin HCl liposome injection should be administered intravenously with an initial rate of 1 mg/min and a (Doxorubicin HCl equivalent) dose of 50 mg/m^2 minimize the risk of infusion reactions. If no infusion related AE's 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 shows any evidence of cardiotoxicity and continues to tolerate treatment. A minimum of 4 courses is recommended because 4 months was the median time to response in clinical trial reports. Adverse events such as Palmar Plantar Erythema (PPE), stomatitis and hematologic toxicity may be managed by delay or reduction in dose. Pretreatment with or concomitant use of antiemetics may be considered.

In AIDS Kaposi syndrome patients, Doxorubicin HCl liposome injection should be administered intravenously with (Doxorubicin HCl equivalent) 20 mg/m^2 over 30 minutes, once every three weeks as long as patients respond satisfactorily and tolerate treatment.

Limited clinical experience exists in treating hepatically impaired patients with i-dox®, however based on experience with Doxorubicin HCl, it is recommended that the dose of i-dox® should be reduced if bilirubin level is elevated. When serum bilirubin is between 1.2 - 3.0 mg/dL administer 1/2 of the normal dose, and when the level is > 3 mg/dL administer 1/4® of the normal dose.

Breast Cancer/Ovarian Cancer Patients

Doxorubicin HCl liposome injection is administered intravenously at a dose of 50 mg/m^2 body surface, once every 4 weeks for as long as the disease does not progress, and the patient shows no evidence of clinical cardiotoxicity and continues to tolerate treatment.

For doses < 90 mg: dilute Doxorubicin HCl liposome injection in 250 mL (50 mg/mL) (5%) Dextrose USP solution for infusion.

For doses ≥90 mg: dilute Doxorubicin HCl liposome injection in 500 mL (50 mg/mL) (5%) Dextrose USP solution for infusion.

The use of any other diluent or the presence of any bacteriostatic agent such as benzyl alcohol may cause precipitation of Doxorubicin HCl liposome injection.

To minimize the risk of infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent Doxorubicin HCl liposome injection infusions may be administered over a 60-minute period.

Patients With Multiple Myeloma

In multiple myeloma patients Bortezomib is administered at a dose of 1.3 mg/m^2 as intravenous bolus on days 1, 4, 8 and 11, every three weeks. On day 4 following bortezomib, Doxorubicin HCl liposome injection 30 mg/m^2 should be administered as a 1-hr intravenous infusion. With the first on day 4 following bortezomib dose, 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. Patients may be treated for up to 8 cycles until disease progression or the occurrence of unacceptable toxicity.

Dose Modification Guidelines have been proposed since Doxorubicin HCl liposome injection exhibits nonlinear pharmacokinetics at 50 mg/m^2. Dose adjustments may thus result in non-proportional greater change in plasma concentration and exposure to the drug. Patients should be carefully monitored for toxicity. Adverse events such as Palmar Plantar Erythema (PPE), hematologic toxicities, and stomatitis may be managed by dose delays and adjustments. Subsequent to the first appearance of a Grade 2 or higher adverse event, dosing should be adjusted and or delayed as described in the following tables and should not be increased at any given time.

Palmar Plantar Erythrodysesthesia

Toxicity Grade	Dose Adjustment
1. Mild erythema, swelling or desquamation not interfering with daily activities.	***Redose unless the patient has experienced previous Grade 3 or 4 toxicity.*** If so, delay upto 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 upto 2 weeks or until resolved to Grade 0-1.*** If after 2 weeks there is no resolution i-dox® should be discontinued
3 Blistering, ulceration or swelling interfering with walking or normal daily activities; regular clothing cannot be worn.	***Delay dosing upto 2 weeks or until resolved to Grade 0-1.*** Decrease dose by 25 % and return to original dose. If after 2 weeks there is no resolution i-dox® should be discontinued.
4 Diffuse or local process causing infectious complications or a bed ridden state or hospitalization.	***Delay dosing upto 2 weeks or until resolved to Grade 0-1.*** Decrease dose by 25 % and return to original dose. If after 2 weeks there is no resolution i-dox® should be discontinued.

Hematological Toxicity

Grade	ANC	Platelets	Modifications
1.	1500 - 1900	75,000 -150,000	Resume treatment with no dose reduction
2.	1000 - < 1500	50000 - < 75,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction.
3.	500 - 999	25,000 - < 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

Stomatitis

Toxicity Grade	Dose Adjustment
1. Painless ulcers, erythema or mild soreness.	***Redose unless the patient has experienced previous Grade 3 or 4 toxicity.*** If so, delay upto 2 weeks and decrease dose by 25 %. Return to original dose interval.
2. Painful erythema, edema or ulcers, but can eat.	***Delay dosing upto 2 weeks or until resolved to Grade 0-1.*** If after 2 weeks there is no resolution i-dox® should be discontinued
3. Painful erythema, edema or ulcers and cannot eat.	***Delay dosing upto 2 weeks or until resolved to Grade 0-1.*** Decrease dose by 25 % and return to original dose. If after 2 weeks there is no resolution i-dox® should be discontinued
4. Requires parenteral or enteral support.	***Delay dosing upto 2 weeks or until resolved to Grade 0-1.*** Decrease dose by 25 % and return to original dose. If after 2 weeks there is no resolution i-dox® should be discontinued.

INDICATION(S)

i-dox® (Doxorubicin HCl liposome injection) is indicated for the treatment of:

Advanced carcinoma of the ovary, in patients with refractory disease (progression of disease while on treatment or within 6 months of completing treatment) to both paclitaxel and platinum based chemotherapy regimens.

AIDS related Kaposi's sarcoma patients showing disease progression, on prior combination chemotherapy or intolerant to therapy.

For the treatment of patients with multiple myeloma in combination with bortezomib, who have not previously received bortezomib and have received at least one prior therapy.

Also indicated for the monotherapy for patients with metastatic breast cancer, where patient is associated with increased cardiac risk with conventional doxorubicin.

The above indications are based on objective tumor response rates, but no results are available from controlled trials that demonstrate clinical benefits resulting from this treatment, such as improvement in disease related symptoms or increased survival.

CONTRAINDICATION(S)

i-dox® (Doxorubicin HCl liposome injection) is contraindicated in patients who have a history of hypersensitivity reactions to conventional Doxorubicin HCl formulation or the components of i-dox®.

i-dox® is contraindicated in nursing mothers.

ADVERSE REACTION(S)

Adverse events observed in ***Ovarian cancer patients*** with an incidence ratio of 1 - 5 % when doses were administered every four weeks are classified below based on the site of reaction/occurrence.

Body as a whole: Allergic reaction, chills, infection, chest pain, back pain, abdomen enlarged and malaise. Cellulitis, anaphylactoid reaction, ascites, flu syndrome, neck pain, moniliasis, injection site pain, face edema, chills, fever, pelvic pain, chest pain

Substernal and injection site inflammation may have incidence ratio less than 1%.

Digestive system: Dyspepsia, oral moniliasis, mouth ulceration, esophagitis and dysphagia. Lesser than 1 % incidence of gingivitis, eructation, increased salivation, melena, gastrointestinal hemorrhage, proctitis, jaundice, ileus, periodontal abscess, flatulence, aphthous stomatitis, gastritis, glossitis and gum hemorrhage may be seen.

Metabolic and nutritional system: Peripheral edema and dehydration. Lesser than 1 % incidence of SGOT increase, creatinine increase, hypocalcemia, hyperglycemia, hypokalemia, hypermagnesemia, hyponatremia, weight gain, bilirubinemia, generalized edema, cachexia and hypochloremia may be seen in patients.

Musculoskeletal System: Myalgia. Arthralgia, bone pain and myasthenia may be seen with less than 1 % incidence.

Nervous System: Somnolence, dizziness, depression, insomnia and anxiety. Lesser than 1 % incidence of peripheral neuritis, incoordination, abnormal thinking, confusion, hypertonia, nervousness, hyperesthesia, hypesthesia, neuropathy and ataxia may be seen.

Respiratory System: Dyspnea, increased cough and rhinitis. Pleural effusion, asthma, hiccup, pneumothorax, laryngitis, sinusitis, voice alteration, epistaxis and pneumonia may be seen with less than 1 % incidence ratio.

Cutaneous: Pruritus, skin discoloration, skin disorder, vesiculobullous rash, maculopapular rash, exfoliative dermatitis, herpes zoster, sweating.

Special Senses: Conjunctivitis and taste perversion. Amblyopia, blepharitis, parosmia and taste loss may be seen with lesser than 1 % incidence.In ovarian cancer patients, lesser than 1 % incidence of AR's may be seen.

Cardiovascular system: Hypertension, angina pectoris, pericardial effusion, postural

hypotension, hypotension, palpitation, syncope, shock, bradycardia, arrhythmia, phlebitis, tachycardia, cardiomegaly, heart failure, hemorrhage.

Hemic and Lymphatic system: Hypochromic anemia, lymphadenopathy, ecchymosis, petechia.

Skin and appendages: skin ulcer, herpes simplex, contact dermatitis, fungal dermatitis, furunculosis, skin nodule, urticaria, acne.

Urogenital system: Urinary tract infection, leukorrhea, cystitis, nocturia, dysuria, breast pain, mastitis, oliguria, vaginitis, kidney function abnormal, vaginal hemorrhage, hydronephrosis, vaginal moniliasis.

Clinical study report among ***AIDS related Kaposi Syndrome patients*** treated with 20 mg/m^2 of Doxorubicin HCl liposome injection every two to three weeks with a median time of 127 days (ranging from 1 - 811 days) and a median cumulative dose of 120 mg/m^2 (ranging from 3.3 - 798.6 mg/m^2) indicate that patients received a variety of potentially myelotoxic drugs such as zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (D4T), sulfamethoxazole/trimethoprim, fluconazole, antivirals, acyclovir, ganciclovir, foscarnet. sargramostim/filgrastim sometime during their course of treatment in combination with Doxorubicin HCl liposome injection. In many instances it was difficult to determine whether adverse events resulted from Doxorubicin HCl liposome injection, from concomitant therapy or from the patients' underlying disease(s). Patients majorly reported occurrence of adverse events to be possibly or probably related to the treatment with i-dox®. Adverse reactions infrequently led to the discontinuation of treatment. Adverse events observed in AIDS related kaposi syndrome patients with an incidence ratio of 1 - 5 % are classified below based on the site of reaction/occurrence.

Body as a Whole: Headache, back pain, infection, allergic reaction and chills. Facial edema, cellulitis, sepsis, abscess, radiation injury, flu syndrome, moniliasis, hypothermia, injection site hemorrhage, injection site pain, cryptococcosis and ascites may be seen with less than 1 % incidence.

Cardiovascular: Chest pain, hypotension and tachycardia. Lesser than 1 % incidence of thrombophlebitis, cardiomyopathy, pericardial effusion, hemorrhage, palpitation, syncope, bundle branch block, congestive heart failure, cardiomegaly, heart arrest, migraine, thrombosis and ventricular arrhythmia may be seen.

Cutaneous: Herpes simplex, rash and itching.

Digestive System: Mouth ulceration, glossitis, constipation, aphthous stomatitis, anorexia, dysphagia and abdominal pain. Dyspepsia, cholestatic jaundice, gastritis, gingivitis, ulcerative proctitis, colitis, esophageal ulcer, esophagitis, gastrointestinal hemorrhage,

Hepatic failure, leukoplakia of mouth, pancreatitis, ulcerative stomatitis, hepatitis, hepatosplenomegaly, increased appetite, jaundice, sclerosing cholangitis, tenesmus, fecal impaction may be seen with less than 1 % incidence.

Hematologic: Hemolysis and increased prothrombin time. Lesser than 1 % incidence of eosinophilia, lymphadenopathy, lymphangitis, lymphedema, petechia, and decrease in thromboplastin may also be seen.

Metabolic/Nutritional: SGPT increase, weight loss, hypocalcemia, hyperbilirubinemia and hyperglycemia. Increase in lactic dehydrogenase, hypernatremia, creatinine increase, BUN increase, dehydration, edema, hypercalcemia, hyperkalemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hypolipemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypoproteinemia, ketosis, weight gain may be seen with less than 1 % incidence.

Other: Dyspnea, albuminuria, pneumonia, retinitis, emotional lability, dizziness and somnolence. In AIDS related Kaposi Syndrome patients lesser than 1 % incidence of AR's may be seen.

Endocrine System: Diabetes mellitus.

Musculoskeletal System: Myalgia, arthralgia, bone pain and myositis.

Nervous System: Paresthesia, insomnia, peripheral neuritis, depression, neuropathy, anxiety, convulsion, hypotonia, acute brain syndrome, confusion, hemiplegia, hypertonia, hypokinesia and vertigo.

Respiratory System: pleural effusion, asthma, bronchitis, cough increase, hyperventilation, pharyngitis, pneumothorax, rhinitis and sinusitis.

Skin and Appendages: Maculopapular rash, skin ulcer, skin discoloration, herpes zoster, exfoliative dermatitis, cutaneous moniliasis, erythema multiforme, erythema nodosum, furunculosis, psoriasis, pustular rash, skin necrosis, urticaria and vesiculobullous rash.

Special Senses: Otitis media, taste perversion, abnormal vision, blindness, conjunctivitis, eye pain, optic neuritis, tinnitus and visual field defect.

Urogenital System: Hematuria, balanitis, cystitis, dysuria, genital edema, glycosuria and kidney failure.

Breast Cancer Patients: 254 advanced breast cancer patients who had not received prior chemotherapy for metastatic disease were treated with Doxorubicin HCl liposome injection at a dose of 50 mg/m^2 body surface, every 4 weeks in a phase III clinical trial. The most frequently reported adverse effects included palmar-plantar erythrodysesthesia (PPE) (48.0%) and nausea (37.0%). Severe (Grade III) cases reported in 17.0% and 3.0% respectively, and no reported incidences of life-threatening (Grade IV) cases for either PPE or nausea. Infrequently, these effects resulted in permanent treatment discontinuation (7.0% and 0% respectively). Pronounced alopecia (or total hair loss) was seen in only 7.0% of Doxorubicin HCl liposome injection treated patients as compared with 54.0% of patients treated with doxorubicin.

Some infrequently reported Hematologic adverse effects were Anemia, neutropenia, leukopenia and thrombocytopenia, were mostly mild or moderate in severity, at incidences of 5.0%, 4.0%, 2.0%, and 1.0%, respectively. Life- threatening (Grade IV) hematologic effects were reported at incidences of <1.0 %. The need for either growth factor support or transfusion support was minimal (5.1% and 5.5% of patients, respectively). Febrile neutropenia was reported in 3/254 (1.2%) patients treated with Doxorubicin HCl liposome injection and 8/255 (3.1%) patients treated with doxorubicin.

Patients With Multiple Myeloma

The safety data below are from 318 patients treated with Doxorubicin HCl liposome injection (30 mg/m^2 as a 1-hr i.v. infusion) administered on day 4 following bortezomib (1.3 mg/m^2 i.v. bolus on days 1, 4, 8 and 11) every three weeks, in a randomized, open-label, multicenter study. In this study, patients were treated for a median number of 138 days (range 21-410 days). The population was 28-85 years of age, 58% male, 42% female, 90% Caucasian, 6% Black, and 4% Asian and other.

Adverse reactions reported in 10% or more of patients treated with Doxorubicin HCl liposome injection in combination with bortezomib for multiple myeloma are given below-

Blood and lymphatic system disorders: Neutropenia, Thrombocytopenia, Anemia.

General disorders and administration site conditions: Fatigue, Pyrexia, Asthenia.

Gastrointestinal disorders: Nausea, Diarrhea, Vomiting, Constipation, Mucositis/Stomatitis, Abdominal pain.

Infections and infestations: Herpes zoster, Herpes simplex.

Investigations: Weight decreased.

Metabolism and Nutritional disorders: Anorexia.

Nervous system disorders: Peripheral Neuropathy (Peripheral neuropathy includes peripheral sensory neuropathy, neuropathy peripheral, polyneuropathy, peripheral motor neuropathy, and neuropathy NOS) , Neuralgia, Paraesthesia/dysesthesia.

Respiratory, thoracic and mediastinal disorders: Cough.