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, DOXULIP 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, DOXULIP 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 DOXULIP original dose interval. If after 2 weeks there is no resolution, DOXULIP should be discontinued.

Multiple Myeloma
For patients treated with liposomal doxorubicin in combination with bortezomib who experience hand-foot syndrome or stomatitis, the liposomal doxorubicin dose should be modified as described in Tables 1 and 3. Table 4 describes dosage adjustments for liposomal doxorubicin and bortezomib combination therapy. For bortezomib dosing and dosage adjustments, see manufacturer's prescribing information.

Table 4: Dosage adjustments for DOXULIP + bortezomib combination therapy

Patient status	DOXULIP	bortezomib
Fever ≥ 38°C and ANC < I,000/mm^3	Do not dose this cycle if before Day 4; if after Day 4, reduce next dose by 25%.	Reduce next dose by 25%
On any day of drug administration after Day 1 of each cycle: Platelet count < 25,000/mm^3 Hemoglobin < 8g/dL ANC < 500/mm^3	Do not dose this cycle if before Day 4; if after Day 4 reduce next dose by 25% in the following cycles if bortezomib is reduced for hematologic toxicity.	Do not dose; if 2 or more doses are not given in a cycle, reduce dose by 25% in following cycles.
Grade 3 or 4 non-hematologic drug related toxicity	Do not dose until recovered to Grade < 2 and reduce dose by 25% for all subsequent doses.	Do not dose until recovered to Grade < 2 and reduce dose by 25% for all subsequent doses.
Neuropathic pain or peripheral neuropathy	No dosage adjustments.	See bortezomib manufacturer's prescribing information for dosage adjustments in patients with neuropathic pain.

Hepatic Impairment
Based on experience with doxorubicin HCl, it is recommended that the liposomal doxorubicin dosage be reduced if the bilirubin is elevated as follows: serum bilirubin 1.2 to 3.0 mg/dL - give ½ normal dose; serum bilirubin > 3 mg/dL - give ¼ normal dose.

Renal Impairment
As doxorubicin is metabolised by the liver and excreted in the bile, dose modification should not be required. Population pharmacokinetic data (in the range of creatinine clearance tested of 30 - 156 ml/min) demonstrate that liposomal doxorubicin clearance is not influenced by renal function. No pharmacokinetic data are available in patients with creatinine clearance of less than 30 ml/min.

Paediatric patients
The experience in children is limited. DOXULIP is not recommended in patients below 18 years of age.

Elderly patients
Population based analysis demonstrates that age across the range tested (21 – 75 years) does not significantly alter the pharmacokinetics of liposomal doxorubicin.

PREPARATION FOR INTRAVENOUS ADMINISTRATION
Liposomal doxorubicin 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 liposomal doxorubicin. Diluted liposomal doxorubicin 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.

DOXULIP 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.

DIRECTIONS
Store in a refrigerator (2° to 8°C). Do not freeze. Protect from light. Keep out of the reach of children.

PRESENTATION
DOXULIP is available as 2mg/ml concentrate solution for infusion in 10ml concentrate solution for injection.
DOXULIP is available as 2mg/ml concentrate solution for infusion in 25ml concentrate solution for injection.

Marketed by:
Revive healthcare
503, 5th Floor, Eden Heights, 6 Main Gulberg, Jail Road, Lahore - Pakistan 54600.

Manufactured by:
United Biotech (P) Limited
Bagbania, Baddi-Nalagarh Road, Distt. Solan (HP) - 174 101 - India

ڈاکسولپ
(ڈاکسوروبسن ہائیڈروکلورائیڈ لیپوسوم انجکشن)
۲۰ ملی گرام انجکشن
کنسنٹریٹ

دوا کو ۲ سے ۸ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔
دوا کو دھوپ اور نمی سے محفوظ رکھیں اور بچنے سے بچائیں۔
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
بچوں کی پہنچ سے دور رکھیں۔

Doxorubicin Hydrochloride Liposome Injection

DOXULIP

(Pegylated Liposomal formulation)
Infusion Concentrate 20mg/10ml & 50mg/25ml

PHARMACEUTICALS WORLDWIDE
UNITED BIOTECH
The Emergence of a New Standard

COMPOSITION
Each ml contains:
Doxorubicin Hydrochloride (As pegylated liposomal) (As per Innovator's Specs.) 2mg

DESCRIPTION
DOXULIP (doxorubicin HCl liposome injection) is doxorubicin hydrochloride (HCl) encapsulated in stealth liposomes for intravenous administration.
Doxorubicin is an anthracycline topoisomerase inhibitor isolated from Streptomyces peucetius var. caesius.
Doxorubicin HCl, which is the established name for (8S,10S)-10-[(3-amino-2,3, 6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycolyl-7,8,9, 10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride. The molecular formula of the drug is $C_{27}H_{29}NO_{11}$•HCl; its molecular weight is 579.99.
DOXULIP is provided as a sterile, translucent, red liposomal dispersion in 10-mL glass, single use vials. Each vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/mL. DOXULIP is doxorubicin HCl encapsulated in long-circulating stealth liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The stealth liposomes are formulated with surface-bound methoxypolyethylene 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.
Stealth 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 remains liposome-encapsulated during circulation.

CLINICAL PHARMACOLOGY
Mechanism of Action
The active ingredient doxorubicin HCl. is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Liposomal doxorubicin demonstrates rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis.
Pharmacokinetics
Liposomal doxorubicin displayed linear pharmacokinetics over the range of 10 to 20 mg/m^2. Disposition occurred in two phases after liposomal doxorubicin 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 liposomal doxorubicin at a 50 mg/m^2 dose is reported to be nonlinear. At this dose, the elimination half-life of liposomal doxorubicin is expected to be longer and the clearance lower compared to a 20 mg/m^2 dose. The exposure (AUC) is thus expected to be more than proportional at a 50 mg/m^2 dose when compared with the lower doses.
Unlike conventional doxorubicin, which displays a large volume of distribution, ranging from 700 to 1100 L/m^2, the small steady state volume of distribution of liposomal doxorubicin shows that liposomal doxorubicin is confined mostly to the vascular fluid volume. Plasma protein binding of liposomal doxorubicin has not been determined; the plasma protein binding of doxorubicin is approximately 70%.
Doxorubicinol, 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/m^2 liposomal doxorubicin.
The plasma clearance of liposomal doxorubicin was slow, with a mean clearance value of 0.041 $L/h/m^2$ at a dose of 20 mg/m^2. Because of its slower clearance, the AUC of liposomal doxorubicin, 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.
No pharmacokinetics study has been done in individuals with renal or hepatic insufficiency.

INDICATIONS

DOXULIP (doxorubicin HCl liposome injection) is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.

DOXULIP (doxorubicin HCl liposome injection) is indicated for the treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.

DOXULIP (doxorubicin HCl liposome injection) in combination with bortezomib is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS

Liposomal doxorubicin HCl injection is contraindicated in patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin HCl or to any component of this preparation.

Liposomal doxorubicin is also contraindicated in nursing mothers.

WARNINGS & PRECAUTIONS

As the experience with the large cumulative doses of liposomal doxorubicn is very limited so special attention must be given to the risk of myocardial damage from cumulative doses of doxorubicin HCl. 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/m^2. Lower (400 mg/m^2) 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 anthracenodiones 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 liposomal doxorubicn only when the potential benefit of treatment outweighs the risk.

Cardiac function should be carefully monitored in patients treated with liposomal doxorubicn. 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 liposomal doxorubicn. If these test results indicate possible cardiac injury associated with liposomal doxorubicn therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

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. 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 resolve 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.

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

Pregnancy & Lactation

Liposomal doxorubicn 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/m^2 human dose on an mg/m^2 basis).

Liposomal doxorubicn can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If liposomal doxorubicn 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 liposomal doxorubicn, the prolonged half-life of the drug must be considered. Women of childbearing potential should be advised to avoid pregnancy during treatment with liposomal doxorubicn.

It is not known whether this drug is excreted in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from liposomal doxorubicn, mothers should discontinue nursing prior to taking this drug.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with liposomal doxorubicn. Liposomal doxorubicn may interact with drugs known to interact with the conventional formulation of doxorubicin Hcl.

SIDE EFFECTS

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

Ovarian Cancer Patients/ Breast Cancer Patients

Incidence 1% to 10%

Cardiovascular: vasodilation, tachycardia, deep thrombophlebitis, hypotension, cardiac arrest. Digestive: oral moniliasis, mouth ulceration, esophagitis, dysphagia, rectal bleeding, ileus. Hemic and Lymphatic: ecchymosis. Metabolic and Nutritional: dehydration, weight loss, hyperbilirubinemia, hypokalemia, hypercalcemia, hyponatremia. Nervous: somnolence, dizziness, depression. Respiratory: rhinitis, pneumonia, sinusitis, epistaxis. Skin and Appendages: pruritus, skin discoloration, vesiculobullous rash, maculopapular rash, exfoliative dermatitis, herpes zoster, dry skin, herpes simplex, fungal dermatitis, furunculosis, acne. Special Senses: conjunctivitis, taste perversion, dry eyes. Urinary: urinary tract infection, hematuria, vaginal moniliasis.

AIDS-Related Kaposi's Sarcoma Patients

Adverse reactions led to discontinuation of treatment in 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.

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.

OVERDOSAGE

Acute overdosage with doxorubicin HCl 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.

DOSAGE AND ADMINISTRATION

Ovarian Cancer/ Breast Cancer

DOXULIP (doxorubicin HCl liposome injection) should be administered intravenously at a dose of 50 mg/m^2 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 responds satisfactory 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. Pretreatment with or concomitant use of antiemetics should be considered.

AIDS-Related Kaposi's Sarcoma

DOXULIP (doxorubicin HCl liposome injection) should be administered intravenously at a dose of 20 mg/m^2. 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.

Multiple Myeloma

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. DOXULIP 30 mg/m^2 should be administered as a 1-hr intravenous infusion on day 4 following bortezomib. With the first DOXULIP 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

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.

Table 1: Hand-Foot Syndrome (HFS)

Toxicity Grade	Dose Adjustment
1 (mild erythema, swelling, or desquamation not interfering with daily activities)	Redose 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, DOXULIP 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, DOXULIP 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, DOXULIP should be discontinued.

Table 2: Hematological Toxicity

Grade	ANC	Platelets	Modification
1	1,500–1,900	75,000 - 150,000	Resume treatment with no dose reduction.
2	1,000 - < 1,500	50,000 - < 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.