Prescription Drug

DOXLOX

Doxorubicin HCl Liposome Injection Concentrate for Solution for Infusion 2 mg/ml (Pegylated liposomal formulation)

Composition:

Each ml of Doxlox contains 2 mg doxorubicin hydrochloride in a pegylated liposomal formulation.

Product Description:

Doxorubicin hydrochloride liposome injection is a translucent, red liposomal dispersion.

Description after Dilution: A translucent red liposomal dispersion.

Clinical Particulars

Therapeutic Indications

Doxorubicin is indicated:

- As monotherapy for patients with metastatic breast cancer

- For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.

- In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.

- For treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (< 200 CD4 lymphocytes/mm3) and extensive mucocutaneous or visceral disease.

Doxorubicin may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline).

Posology and Method of administration

Doxorubicin should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic agents.

Doxorubicin exhibits unique pharmacokinetic properties and must not be used interchangeably with other formulations of doxorubicin hydrochloride.

Posology

Breast cancer/Ovarian cancer

Doxorubicin is administered intravenously at a dose of 50 mg/m^2 once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment.

Multiple myeloma

Doxorubicin is administered at 30 mg/m² on day 4 of the bortezomib 3 week regimen as a 1 hour infusion administered immediately after the bortezomib infusion. The bortezomib regimen consists of 1.3 mg/m² on days 1, 4, 8, and 11 every 3 weeks. The dose should be repeated as long as patients respond satisfactorily and tolerate treatment.

AIDS-KS patients

Doxorubicin should be administered intravenously at 20 mg/m^2 every two-to-three weeks. Intervals shorter than 10 days should be avoided as drug accumulation and increased toxicity cannot be ruled out. Patients should be treated for two-to-three months to achieve a therapeutic response. Treatment should be continued as needed to maintain a therapeutic response.

Guidelines for Doxorubicin dose modification

To manage adverse events such as palmar-plantar erythrodysesthesia (PPE), stomatitis or haematological toxicity, the dose may be reduced or delayed. Guidelines for Doxorubicin dose modification secondary to these adverse effects are provided in the tables below. The toxicity grading in these tables is based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

The tables for PPE (Table 1) and stomatitis (Table 2) provide the schedule followed for dose modification in clinical trials in the treatment of breast or ovarian cancer (modification of the recommended 4 week treatment cycle): if these toxicities occur in patients with AIDS-related KS, the recommended 2 to 3 week treatment cycle can be modified in a similar manner.

The table for haematological toxicity (Table 3) provides the schedule followed for dose modification in clinical trial in the treatment of patients with breast or ovarian cancer only. Dose modification in patients with AIDS-KS is addressed in Adverse Reactions.

Table 1. Palmar-Plantar erythrodysesthesia

	Week after prior Doxorubicin dose		
Toxicity grade at current assessment	**Week 4**	**Week 5**	**Week 6**
Grade 1 (mild erythema, swelling, or desquamation not interfering with daily activities)	**Redose unless** Patient has experienced a previous grade 3 or 4 skin toxicity, in which case wait an additional week	**Redose unless** Patient has experienced a previous grade 3 or 4 skin toxicity, in which case wait an additional week	**Decrease dose by 25%; return to 4 week interval**
Grade 2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter)	**Wait an additional week**	**Wait an additional week**	**Decrease dose by 25%; return to 4 week interval**

Grade 3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	**Wait an additional week**	**Wait an additional week**	**Discontinue Doxorubicin**
Grade 4 (diffuse or local process causing infectious complications, or a bedridden state or hospitalisation)	**Wait an additional week**	**Wait an additional week**	**Discontinue Doxorubicin**

Table 2. Stomatitis

	Week after prior Doxorubicin dose		
Toxicity grade at current assessment	**Week 4**	**Week 5**	**Week 6**
Grade 1 (painless ulcers, erythema, or mild soreness)	**Redose unless** patient has experienced a previous grade 3 or 4 stomatitis in which case wait an additional week	**Redose unless** patient has experienced a previous grade 3 or 4 stomatitis in which case wait an additional week	**Decrease dose by 25%; return to 4 week interval** or withdraw patient per physician's assessment
Grade 2 (painful erythema, oedema, or ulcers, but can eat)	**Wait an additional week**	**Wait an additional week**	**Decrease dose by 25%; return to 4 week interval** or withdraw patient per physician's assessment
Grade 3 (painful erythema, edema, or ulcers, but cannot eat)	**Wait an additional week**	**Wait an additional week**	**Discontinue Doxorubicin**
Grade 4 (requires parenteral or enteral support)	**Wait an additional week**	**Wait an additional week**	**Discontinue Doxorubicin**

Table 3. Haematological toxicity (ANC or platelets) - Management of patients with breast or ovarian cancer

GRADE	**ANC**	**PLATELETS**	**MODIFICATION**

Grade 1	1,500 – 1,900	75,000 – 150,000	Resume treatment with no dose reduction.
Grade 2	1,000 – < 1,500	50,000 – < 75,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction.
Grade 3	500 – < 1,000	25,000 – < 50,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction.
Grade 4	< 500	< 25,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; decrease dose by 25% or continue full dose with growth factor support.

For multiple myeloma patients treated with Doxorubicin in combination with bortezomib who experience PPE or stomatitis, the Doxorubicin dose should be modified as described in Table 1 and 2 above respectively. For more detailed information on bortezomib dosing and dosage adjustments, see the prescribing information for bortezomib.

Table 4. Dosage adjustments for Doxorubicin + bortezomib combination therapy - patients with multiple myeloma

Patient status	**Doxorubicin**	**Bortezomib**
Fever ≥ 38°C and ANC < 1,000/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 medicine administration after day 1 of each cycle: Platelet count < 25,000/mm^3 Hemoglobin < 8 g/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 medicine 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 the SPC for bortezomib.

***** for more information on bortezomib dosing and dosage adjustment, see the SPC for bortezomib

Special Populations

Pediatrics (17 years of age and younger)

Limited Phase I safety data indicate that doses up to 60 mg/m2 every 4 weeks are well tolerated in pediatric patients; however, effectiveness in patients under 18 years of age has not been established.

Elderly (65 years of age and older)

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

Patients with impaired renal function

As doxorubicin is metabolised by the liver and excreted in the bile, dose modification should not be required with Doxorubicin. Population-based analysisconfirms that changes in renal function over the range tested (estimated creatinine clearance 30-156 mL/min) do not alter the pharmacokinetics of doxorubicin. No pharmacokinetic data are available in patients with creatinine clearance of less than 30 ml/min.

Hepatic impairment

doxorubicin pharmacokinetics determined in a small number of patients with elevated total bilirubin levels do not differ from patients with normal total bilirubin; however, until further experience is gained, the doxorubicin dosage in patients with impaired hepatic function should be reduced based on the experience from the breast and ovarian clinical trial program as follows: At initiation of therapy, if the bilirubin is between 1.2 - 3.0 mg/dl, the first dose is reduced by 25 %. If the bilirubin is > 3.0 mg/dL, the first dose is reduced by 50 %. If the patient tolerates the first dose without an increase in serum bilirubin or liver enzymes, the dose for cycle 2 can be increased to the next dose level, i.e., if reduced by 25 % for the first dose, increase to full dose for cycle 2; if reduced by 50 % for the first dose, increase to 75 % of full dose for cycle 2.The dosage can be increased to full dose for subsequent cycles if tolerated. Doxorubicin can be administered to patients with liver metastases with concurrent elevation of bilirubin and liver enzymes up to 4 ×the upper limit of the normal range. Prior to doxorubicin administration, evaluate hepatic function using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase, and bilirubin.

Other population

AIDS-KS patients with splenectomy: As there is no experience with doxorubicin in patients with splenectomy, treatment with doxorubicin is not recommended.

Method of administration

For doses < 90 mg: dilute Doxorubicin in 250 ml Dextrose 5% in water

For doses ≥ 90 mg: dilute Doxorubicin in 500 ml Dextrose 5% in water.

If the patient experiences early symptoms or signs of infusion reaction, immediately discontinue the infusion, give appropriate premedications (antihistamine and/or short acting corticosteroid) and restart at a slower rate.

DO NOT administer as a bolus injection or undiluted solution. It is recommended that the doxorubicin infusion line be connected through the side port of an intravenous infusion of Dextrose 5% in Water to achieve further dilution and minimize the risk of thrombosis and extravasation. The infusion may be given through a peripheral vein. Doxorubicin must not be given by the intramuscular or subcutaneous route. Do not use with in-line filters.

Breast cancer/Ovarian cancer

To minimise 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 infusions may be administered over a 60-minute period.

In the breast cancer trial program, modification of the infusion was permitted for those patients experiencing an infusion reaction as follows:5% of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate was doubled for the next 15 minutes. If tolerated, the infusion was completed over the next hour for a total infusion time of 90 minutes. Subsequent doxorubicin infusions may be administered over a 60 minute period.

Multiple myeloma

The intravenous catheter and tubing should be flushed with 5% glucose solution for infusion between administration of doxorubicin and bortezomib. Day 4 dosing of both medicinal products may be delayed up to 48 hours as medically necessary. Doses of bortezomib should be at least 72 hours apart. The first infusion of doxorubicin should be administered over 90 minutes, as follows:

1. 10 mL over first 10 minutes

2. 20 mL over next 10 minutes

3. 40 mL over next 10 minutes

4. Then, complete the infusion over a total of 90 minutes.

Subsequent doses of doxorubicin will be administered over 1 hour, as tolerated. If an infusion reaction to doxorubicin occurs, stop the infusion and after the symptoms resolve, attempt to administer the remaining doxorubicin over 90 minutes, as follows:

5. 10 mL over first 10 minutes

6. 20 mL over next 10 minutes

7. 40 mL over next 10 minutes

8. then, complete the remaining infusion over a total of 90 minutes. Infusion may be given through a peripheral vein or a central line.

AIDS-related KS

Doxorubicin, diluted in 250 ml Dextrose 5% in water, is administered by intravenous infusion over 30 minutes.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Doxorubicin must not be used to treat AIDS-KS that may be treated effectively with local therapy or systemic alfa-interferon.

Special warnings and precautions for use

Given the difference in pharmacokinetic profiles and dosing schedules, doxorubicin should not be used interchangeably with other formulations of doxorubicin hydrochloride.

Cardiac toxicity

It is recommended that all patients receiving Doxorubicin routinely undergo frequent ECG monitoring. Transient ECG changes such as T-wave flattening, S-T segment depression and benign arrhythmias are not considered mandatory indications for the suspension of Doxorubicin therapy. However, reduction of the QRS complex is considered more indicative of cardiac toxicity. If this change occurs, the most definitive test for anthracycline myocardial injury, i.e., endomyocardial biopsy, must be considered.

More specific methods for the evaluation and monitoring of cardiac functions as compared to ECG are a measurement of left ventricular ejection fraction by echocardiography or preferably by Multigated Angiography (MUGA). These methods must be applied routinely before the initiation of Doxorubicin therapy and repeated periodically during treatment. The evaluation of left ventricular function is considered to be mandatory before each additional administration of Doxorubicin that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2.

The evaluation tests and methods mentioned above concerning the monitoring of cardiac performance during anthracycline therapy are to be employed in the following order: ECG monitoring, measurement of left ventricular ejection fraction, endomyocardial biopsy. If a test result indicates possible cardiac injury associated with Doxorubicin therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

In patients with cardiac disease requiring treatment, administer doxorubicin only when the benefit outweighs the risk to the patient.

Exercise caution in patients with impaired cardiac function who receive Doxorubicin.

Whenever cardiomyopathy is suspected, i.e., the left ventricular ejection fraction has substantially decreased relative to pre-treatment values and/or left ventricular ejection fraction is lower than a prognostically relevant value, endomyocardial biopsy may be considered and the benefit of continued therapy must be carefully evaluated against the risk of developing irreversible cardiac damage.

Congestive heart failure due to cardiomyopathy may occur suddenly, without prior ECG changes and may also be encountered several weeks after discontinuation of therapy.

Caution must be observed in patients who have received other anthracyclines. The total dose of doxorubicin hydrochloride must also take into account any previous (or concomitant) therapy with cardiotoxic compounds such as other anthracyclines/anthraquinones or e.g., 5-fluorouracil. Cardiac toxicity also may occur at cumulative anthracycline doses lower than 450 mg/m^2 in patients with prior mediastinal irradiation or in those receiving concurrent cyclophosphamide therapy.

The cardiac safety profile for the dosing schedule recommended for both breast and ovarian cancer (50 mg/m^2) is similar to the 20 mg/m^2 profile in patients with AIDS-KS.

<u>Myelosuppression</u>

Many patients treated with Doxorubicin have baseline myelosuppression due to such factors as their pre-existing HIV disease or numerous concomitant or previous medications, or tumours involving bone marrow. Myelosuppression was generally mild to moderate, reversible, and was not associated with episodes of neutropaenic infection or sepsis in patients with ovarian cancer treated at a dose of 50 mg/m^2. Myelosuppression appears to be the dose-limiting adverse event in patients with AIDS-KS, breast cancer or ovarian cancer. Because of the potential for bone marrow

suppression, periodic blood counts must be performed frequently during the course of Doxorubicin therapy, and at a minimum, prior to each dose of Doxorubicin.

Persistent severe myelosuppression, may result in superinfection or haemorrhage.

In patients with AIDS-KS against a bleomycin/vincristine regimen, opportunistic infections were apparently more frequent during treatment with Doxorubicin. Patients and doctors must be aware of this higher incidence and take action as appropriate.

Secondary haematological malignancies

As with other DNA-damaging antineoplastic agents, secondary acute myeloid leukemias and myelodysplasias have been reported in patients having received combined treatment with doxorubicin. Therefore, any patient treated with doxorubicin should be kept under haematological supervision.

Secondary oral neoplasms

Very rare cases of secondary oral cancer have been reported in patients with long-term (more than one year) exposure to Doxorubicin or those receiving a cumulative Doxorubicin dose greater than 720 mg/m^2. Cases of secondary oral cancer were diagnosed both, during treatment with Doxorubicin, and up to 6 years after the last dose. Patients should be examined at regular intervals for the presence of oral ulceration or any oral discomfort that may be indicative of secondary oral cancer.

Infusion-associated reactions

Serious and sometimes life-threatening infusion reactions, which are characterised by allergic-like or anaphylactoid-like reactions, with symptoms including asthma, flushing, urticarial rash, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial edema, chills, and back pain, tightness in the chest and throat and/or hypotension may occur within minutes of starting the infusion of Doxorubicin. Very rarely, convulsions also have been observed in relation to infusion reactions. Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medications to treat these symptoms (e.g., antihistamines, corticosteroids, adrenaline, and anticonvulsants), as well as emergency equipment should be available for immediate use. In most patients treatment can be resumed after all symptoms have resolved, without recurrence. Infusion reactions rarely recur after the first treatment cycle. To minimise the risk of infusion reactions, the initial dose should be administered at a rate no greater than 1 mg/minute.

Diabetic patients

Please note that each vial of Doxorubicin contains sucrose and the dose is administered in 5% (50 mg/ml) glucose solution for infusion.

Interaction with other medicinal products and other forms of interaction

Exercise caution in the concomitant use of medicinal products known to interact with standard doxorubicin hydrochloride. Doxorubicin, like other doxorubicin hydrochloride preparations, may potentiate the toxicity of other anti-cancer therapies. In patients with solid tumours (including breast and ovarian cancer) who have received concomitant cyclophosphamide or taxanes, no new additive toxicities were noted. In patients with AIDS**,** exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been

reported with standard doxorubicin hydrochloride. Caution must be exercised when giving any other cytotoxic agents, especially myelotoxic agents, at the same time.

Fertility, pregnancy and lactation

Pregnancy

Doxorubicin hydrochloride is suspected to cause serious birth defects when administered during pregnancy. Therefore, Doxorubicin should not be used during pregnancy unless clearly necessary.

Women of child-bearing potential

Women of child-bearing potential must be advised to avoid pregnancy while they or their male partner are receiving Doxorubicin and in the six months following discontinuation of Doxorubicin therapy.

Breast-feeding

It is not known whether Doxorubicin is excreted in human milk. Because many medicinal products, including anthracyclines, are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, therefore mothers must discontinue nursing prior to beginning Doxorubicin treatment. Health experts recommend that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

The effect of doxorubicin hydrochloride on human fertility has not been evaluated.

Effects on ability to drive and use machines

Doxorubicin has no or negligible influence on the ability to drive and use machines. Dizziness and somnolence were associated infrequently with the administration of Doxorubicin. Patients who suffer from these effects must avoid driving and operating machinery.

Undesirable effects

Summary of the safety profile

The most common undesirable effect reported in breast/ovarian patients (50 mg/m^2 every 4 weeks) was palmar-plantar erythrodysesthesia (PPE). PPE is characterised by painful, macular reddening skin eruptions. In patients experiencing this event, it is generally seen after two or three cycles of treatment. Improvement usually occurs in one - two weeks, and in some cases, may take up to 4 weeks or longer for complete resolution. Pyridoxine at a dose of 50-150 mg per day and corticosteroids have been used for the prophylaxis and treatment of PPE. Other strategies to prevent and treat PPE include keeping hands and feet cool, by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight fitting). PPE appears to be primarily related to the dose schedule and can be reduced by extending the dose interval 1-2 weeks. However, this reaction can be severe and debilitating in some patients and may require discontinuation of treatment. Stomatitis/mucositis and nausea were also commonly reported in breast/ovarian cancer patient populations, whereas the AIDS-KS Program (20 mg/m^2 every 2 weeks), myelosuppression (mostly leukopaenia) was the most common side effect. The most frequently reported (medicine-related treatment-emergent) adverse events in combination therapy (doxorubicin + bortezomib) were nausea, diarrhoea, neutropaenia, thrombocytopaenia, vomiting, fatigue, and constipation.

Breast cancer

The following common adverse events were reported more often with doxorubicin at a dose of 50 mg/m^2 every 4 weeks than with Doxorubicin 60 mg/m^2 every 3 weeks: nausea, vomiting, any alopecia, pronounced alopecia, and neutropaenia.

Mucositis and stomatitis were reported more commonly with Doxorubicin than with doxorubicin. The average duration of the most common severe (grade 3/4) events for both groups was 30 days or less. See Table 5 for complete listing of undesirable effects reported in Doxorubicin -treated patients.

The incidence of life threatening (grade 4) haematologic effects and sepsis was reported. Growth factor support or transfusion support was necessary.

Clinically significant laboratory abnormalities (grades 3 and 4) in this group was low with elevated total bilirubin, AST and ALT reported. No clinically significant increases in serum creatinine were reported.

Table 5. Treatment related undesirable effects reported in breast cancer (50 mg/m^2 every 4 weeks) (Doxorubicin -treated patients) by Very common; Common; Uncommon

AE by body system	Breast cancer All severities	Breast cancer Grades 3/4	Breast cancer not previously reported
Infections and infestations			
Common	Pharyngitis		Folliculitis, fungal infection, cold sores (non-herpetic), upper respiratory tract infection
Uncommon		Pharyngitis	
Blood and lymphatic system disorders			
Common	Leukopaenia, anaemia, neutropaenia, thrombocytopaenia	Leukopaenia, anaemia	Thrombocythemia
Uncommon		Neutropaenia	
Metabolism and nutrition disorders			
Very common	Anorexia		
Common		Anorexia	
Nervous system disorders			
Common	Paresthesia	Paresthesia	Peripheral neuropathy
Uncommon	Somnolence		

Eye disorders			
Common			Lacrimation, blurred vision
Cardiac disorders			
Common			Ventricular arrhythmia
Respiratory, thoracic and mediastinal disorders			
Common			Epistaxis
Gastrointestinal disorders			
Very common	Nausea, stomatitis, vomiting		
Common	Abdominal pain, constipation, diarrhoea, dyspepsia, mouth ulceration	Abdominal pain, diarrhoea, nausea, stomatitis	Oral pain
Uncommon		Mouth ulceration, constipation, vomiting	
Skin and subcutaneous tissue disorders			
Very common	PPE*, alopecia, rash	PPE*	
Common	Dry skin, skin discolouration, pigmentation abnormal, erythema	Rash	Bullous eruption, dermatitis, erythematous rash, nail disorder, scaly skin
Uncommon		Pigmentation abnormal, erythema	
Musculoskeletal and connective tissue disorders			
Common			Leg cramps, bone pain, musculoskeletal pain
Reproductive system and breast disorders			
Common			Breast pain
General disorders and administration site conditions			
Very common	Asthenia, fatigue, mucositis NOS		

Common	Weakness, fever, pain	Asthenia, mucositis NOS	Oedema, leg oedema.
Uncommon		Fatigue, weakness, pain	

* Palmar-plantar erythrodysesthesia (Hand-foot syndrome).

Ovarian cancer

Patients with ovarian cancer (a subset of 876 solid tumour patients) were treated with Doxorubicin at a dose of 50 mg/m^2. See Table 6 for undesirable effects reported in Doxorubicin -treated patients.

Table 6. Treatment related undesirable effects reported in ovarian cancer (50 mg/m^2 every 4 weeks) (Doxorubicin -treated patients) by severity.

AE by body system	Ovarian cancer All severities	Ovarian cancer Grades 3/4	Ovarian cancer
Infections and infestations			
Common	Pharyngitis		Infection, oral moniliasis, herpes zoster, urinary tract infection
Uncommon		Pharyngitis	
Blood and lymphatic system disorders			
Very common	Leukopaenia, anaemia, neutropaenia, thrombocytopaenia	Neutropaenia	
Common		Leukopaenia, anaemia, thrombocytopaenia	Hypochromic anaemia
Immune system disorders			
Common			Allergic reaction
Metabolism and nutrition disorders			
Very common	Anorexia		
Common			Dehydration, cachexia
Uncommon		Anorexia	
Psychiatric disorders			
Common			Anxiety, depression, insomnia
Nervous system disorders			

Common	Paresthesia, somnolence		Headache, dizziness, neuropathy, hypertonia
Uncommon		Paresthesia, somnolence	
Eye disorders			
Common			Conjunctivitis
Cardiac disorders			
Common			Cardiovascular disorder
Vascular disorders			
Common			Vasodilatation
Respiratory, thoracic and mediastinal disorders			
Common			Dyspnoea, increased cough
Gastrointestinal disorders			
Very common	Constipation, diarrhoea, nausea, stomatitis, vomiting		
Common	Abdominal pain, dyspepsia, mouth ulceration	Nausea, stomatitis, vomiting, abdominal pain, diarrhoea	Mouth ulceration, esophagitis, nausea and vomiting, gastritis, dysphagia, dry mouth, flatulence, gingivitis, taste perversion
Uncommon		Constipation, dyspepsia, mouth ulceration	
Skin and subcutaneous tissue disorders			
Very common	PPE*, alopecia, rash	PPE*	
Common	Dry skin, skin discolouration	Alopecia, rash	Vesiculobullous rash, pruritus, exfoliative dermatitis, skin disorder, maculopapular rash, sweating, acne, skin ulcer
Musculoskeletal and connective tissue disorders			
Common			Back pain, myalgia
Renal and urinary disorders			
Common			Dysuria

Not Known	Renal-limited thrombotic microangiopathy		
Reproductive system and breast disorders			
Common			Vaginitis
General disorders and administration site conditions			
Very common	Asthenia, mucous membrane disorder		
Common	Fever, pain	Asthenia, mucous membrane disorder, pain	Chills, chest pain, malaise, peripheral oedema
Uncommon		Fever	
Investigations			
Common			Weight loss

* Palmar-plantar erythrodysesthesia (Hand-foot syndrome).

Myelosuppression was mostly mild or moderate and manageable. Sepsis related to leukopaenia was observed infrequently. Growth factor support was required infrequently and transfusion support was required in approximately 15% of patients.

In patients with ovarian cancer, increases in total bilirubin (usually in patients with liver metastases) and serum creatinine levels. Increases in AST were less frequently reported.

Multiple myeloma

patients with multiple myeloma who have received at least 1 prior therapy, treated with combination therapy of Doxorubicin 30 mg/m^2 as a one hour intravenous infusion administered on day 4 following bortezomib which is administered at 1.3 mg/m^2 on days 1, 4, 8, and 11, every three weeks or with bortezomib monotherapy. See Table 7 for adverse effects reported in patients treated with combination therapy of Doxorubicin plus bortezomib.

Neutropaenia, thrombocytopaenia, and anaemia were the most frequently reported hematologic events reported with both combination therapy of Doxorubicin plus bortezomib and bortezomib monotherapy. The incidence of grade 3 and 4 neutropaenia was higher in the combination therapy group than in the monotherapy group. The incidence of grade 3 and 4 thrombocytopaenia was higher in the combination therapy group than in the monotherapy group. The incidence of anaemia was similar in both treatment groups.

Stomatitis was reported more frequently in the combination therapy group than in the monotherapy group, and most cases were grade 2 or less in severity. Grade 3 stomatitis was reported in patients in the combination therapy group. No grade 4 stomatitis was reported.

Nausea and vomiting were reported more frequently in the combination therapy group than in the monotherapy group and were mostly grade 1 and 2 in severity.

Treatment discontinuation of one or both agents due to adverse events was seen in 38% of patients. Common adverse events which led to treatment discontinuation of bortezomib and Doxorubicin

included PPE, neuralgia, peripheral neuropathy, peripheral sensory neuropathy, thrombocytopaenia, decreased ejection fraction, and fatigue.

Table 7. Treatment related undesirable effects reported in multiple myeloma (Doxorubicin 30 mg/m^2 in combination with bortezomib every 3 weeks) by severity

AE by body system	All Severities	Grades 3/4**	All Severities
Infections and infestations			
Common	Herpes simplex, herpes zoster	Herpes zoster	Pneumonia, nasopharyngitis, upper respiratory tract infection, oral candidiasis
Blood and lymphatic system disorders			
Very common	Anaemia, neutropaenia, thrombocytopaenia	Neutropaenia, thrombocytopaenia	
Common	Leukopaenia	Anaemia, leukopaenia	Febrile neutropaenia, lymphopaenia
Metabolism and nutrition disorders			
Very common	Anorexia		
Common	Decreased appetite	Anorexia	Dehydration, hypokalaemia, hyperkalaemia, hypomagnesaemia, hyponatraemia, hypocalcaemia
Uncommon		Decreased appetite	
Psychiatric disorders			
Common	Insomnia		Anxiety
Nervous system disorders			
Very common	Peripheral sensory neuropathy, neuralgia, headache		
Common	Neuropathy peripheral, neuropathy, paraesthesia, polyneuropathy, dizziness, dysgeusia	Neuralgia, peripheral neuropathy, neuropathy	Lethargy, hypoaesthesia, syncope, dysaesthesia

Uncommon		Headache, peripheral sensory neuropathy, paraesthesia, dizziness	
Eye disorders			
Common			Conjunctivitis
Vascular disorders			
Common			Hypotension, orthostatic hypotension, flushing, hypertension, phlebitis
Respiratory, thoracic and mediastinal disorders			
Common	Dyspnoea		Cough, epistaxis exertional dyspnoea
Uncommon		Dyspnoea	
Gastrointestinal disorders			
Very common	Nausea, diarrhoea, vomiting, constipation, stomatitis		
Common	Abdominal pain, dyspepsia	Nausea, diarrhoea, vomiting, stomatitis	Upper abdominal pain, mouth ulceration, dry mouth, dysphagia, aphthous stomatitis
Uncommon		Constipation, abdominal pain, dyspepsia	
Skin and subcutaneous tissue disorders			
Very common	PPE*, rash		
Common	Dry skin	PPE*	Pruritus, papular rash, allergic dermatitis, erythema, skin hyperpigmentation, petechiae, alopecia, medicine eruption
Uncommon		Rash	

Musculoskeletal and connective tissue disorders			
Common	Pain in extremity		Arthralgia, myalgia, muscle spasms, muscular weakness, musculoskeletal pain, musculoskeletal chest pain
Reproductive system and breast disorders			
Common			Scrotal erythema
General disorders and administration site conditions			
Very common	Asthenia, fatigue, pyrexia		
Common		Asthenia, fatigue	Peripheral oedema, chills, influenza-like illness, malaise, hyperthermia
Uncommon		Pyrexia	
Investigations			
Common	Weight decreased		Aspartate aminotransferase increased, ejection fraction decreased, blood creatinine increased, alanine aminotransferase increased

* Palmar-plantar erythrodysesthesia (Hand-foot syndrome).

** Grade 3/4 adverse events are based on the adverse event terms of all severities with an overall incidence ≥ 5% (see adverse events listed in first column).

AIDS-related KS

AIDS-KS patients treated at 20 mg/m^2 with Doxorubicin show that myelosuppression was the most frequent undesirable effect considered related to Doxorubicin occurring very commonly.

Leukopaenia is the most frequent undesirable effect experienced with Doxorubicin in this population; neutropaenia, anaemia and thrombocytopaenia have been observed. These effects may occur early on in treatment. Haematological toxicity may require dose reduction or suspension or delay of therapy. Temporarily suspend Doxorubicin treatment in patients when the ANC count is < 1,000/mm^3 and/or the platelet count is < 50,000/mm^3. G-CSF (or GM-CSF) may be given as concomitant therapy to support the blood count when the ANC count is < 1,000/mm^3 in subsequent cycles. The haematological toxicity for ovarian cancer patients is less severe than in the AIDS-KS.

Respiratory undesirable effects commonly occurred with Doxorubicin and may be related to opportunistic infections in the AIDS population. Opportunistic infections (OI's) are observed in KS patients after administration with Doxorubicin, and are frequently observed in patients with HIV-induced immunodeficiency. The most frequently observed OI's were candidiasis, cytomegalovirus, herpes simplex, *Pneumocystis carinii* pneumonia, and mycobacterium avium complex.

Table 8. Undesirable effects observed in patients with AIDS-related KS

Infections and infestations	
common	oral moniliasis
Blood and lymphatic system disorders	
very common	neutropaenia, anaemia, leukopaenia
common	thrombocytopaenia
Metabolism and nutrition disorders	
common	anorexia
Psychiatric disorders	
uncommon	confusion
Nervous system disorders	
common	dizziness
uncommon	paresthesia
Eye disorders	
common	retinitis
Vascular disorders	
common	Vasodilatation
Respiratory, thoracic and mediastinal disorders	
common	Dyspnoea
Gastrointestinal disorders	
very common	Nausea
common	Diarrhoea, stomatitis, vomiting, mouth ulceration, abdominal pain, glossitis, constipation, nausea and vomiting
Skin and subcutaneous tissue disorders	
common	Alopecia, rash
uncommon	palmar-plantar erythrodysesthesia (PPE)
General disorders and administration site conditions	

common	Asthenia, fever, infusion-associated acute reactions
Investigations	
common	weight loss

Other less frequently observed undesirable effects included hypersensitivity reactions including anaphylactic reactions. Following marketing, bullous eruption has been reported rarely in this population.

Clinically significant laboratory abnormalities frequently occurred including increases in alkaline phosphatase; AST and bilirubin which were believed to be related to the underlying disease and not Doxorubicin. Reduction in haemoglobin and platelets were less frequently reported. Sepsis related to leukopaenia was rarely observed. Some of these abnormalities may have been related to the underlying HIV infection and not Doxorubicin.

All patients

Patients with solid tumours were described as having an infusion-associated reaction during treatment with Doxorubicin as defined by the following Costart terms: allergic reaction, anaphylactoid reaction, asthma, face oedema, hypotension, vasodilatation, urticaria, back pain, chest pain, chills, fever, hypertension, tachycardia, dyspepsia, nausea, dizziness, dyspnoea, pharyngitis, rash, pruritus, sweating, injection site reaction and medicinal product interaction. Permanent treatment discontinuation was infrequently reported. A similar incidence of infusion reactions and treatment discontinuation was observed in the breast cancer program**.** In patients with multiple myeloma receiving Doxorubicin plus bortezomib, infusion-associated reactions have been reported. In patients with AIDS-KS, infusion-associated reactions, were characterised by flushing, shortness of breath, facial oedema, headache, chills, back pain, tightness in the chest and throat and/or hypotension. Very rarely, convulsions have been observed in relation to infusion reactions. In all patients, infusion-associated reactions occurred primarily during the first infusion. Temporarily stopping the infusion usually resolves these symptoms without further therapy. In nearly all patients, Doxorubicin treatment can be resumed after all symptoms have resolved without recurrence. Infusion reactions rarely recur after the first treatment cycle with Doxorubicin.

Myelosuppression associated with anaemia, thrombocytopaenia, leukopaenia, and rarely febrile neutropaenia, has been reported in Doxorubicin -treated patients.

Stomatitis has been reported in patients receiving continuous infusions of conventional doxorubicin hydrochloride and was frequently reported in patients receiving Doxorubicin. It did not interfere with patients completing therapy and no dosage adjustments are generally required, unless stomatitis is affecting a patient's ability to eat. In this case, the dose interval may be extended by 1-2 weeks or the dose reduced.

An increased incidence of congestive heart failure is associated with doxorubicin therapy at cumulative lifetime doses > 450 mg/m^2 or at lower doses for patients with cardiac risk factors. Endomyocardial biopsies on nine of ten AIDS-KS patients receiving cumulative doses of Doxorubicin greater than 460 mg/m^2 indicate no evidence of anthracycline-induced cardiomyopathy. The recommended dose of Doxorubicin for AIDS-KS patients is 20 mg/m^2 every two-to-three weeks. The cumulative dose at which cardiotoxicity would become a concern for

these AIDS-KS patients (> 400 mg/m^2) would require more than 20 courses of Doxorubicin therapy over 40 to 60 weeks.

In addition, endomyocardial biopsies were performed in 8 solid tumour patients with cumulative anthracycline doses of 509 mg/m^2–1,680 mg/m^2. The range of Billingham cardiotoxicity scores was grades 0-1.5. These grading scores are consistent with no or mild cardiac toxicity.

Cardiac toxicity was defined as a decrease of 20 points or greater from baseline if the resting LVEF remained in the normal range or a decrease of 10 points or greater if the LVEF became abnormal (less than the lower limit for normal).

In patients with solid tumours, including a subset of patients with breast and ovarian cancers, treated at a dose of 50 mg/m^2/cycle with lifetime cumulative anthracycline doses up to 1,532 mg/m^2, the incidence of clinically significant cardiac dysfunction was low.

As with other DNA-damaging antineoplastic agents, secondary acute myeloid leukemias and myelodysplasias have been reported in patients having received combined treatment with doxorubicin. Therefore, any patient treated with doxorubicin should be kept under haematological supervision.

Although local necrosis following extravasation has been reported very rarely, Doxorubicin is considered to be an irritant. Animal studies indicate that administration of doxorubicin hydrochloride as a liposomal formulation reduces the potential for extravasation injury. If any signs or symptoms of extravasation occur (e.g., stinging, erythema) terminate the infusion immediately and restart in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. Doxorubicin must not be given by the intramuscular or subcutaneous route.

Recall of skin reaction due to prior radiotherapy has rarely occurred with Doxorubicin administration.

Post-marketing experience

Adverse drug reactions identified during the post-marketing experience with Doxorubicin are described in Table 9. The frequencies are provided according to the following convention:

Very common; Common and Uncommon; Rare; Very rare including isolated reports

Table 9. Adverse drug reactions identified during the post-marketing experience with Doxorubicin

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
very rare	secondary oral neoplasms[1]
Vascular disorders	
uncommon	venous thromboembolism, including thrombophlebitis, venous thrombosis and pulmonary embolism
Skin and subcutaneous tissue disorders	
very rare	erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis

[1] Cases of secondary oral cancer have been reported in patients with long-term (more than one year) exposure to Doxorubicin or those receiving a cumulative Doxorubicin dose greater than 720 mg/m^2.

Overdose

Acute overdosing with doxorubicin hydrochloride worsens the toxic effects of mucositis, leukopaenia and thrombocytopaenia. Treatment of acute overdose of the severely myelosuppressed patient consists of hospitalisation, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances).

Mechanism of action

The active ingredient of doxorubicin is doxorubicin hydrochloride, a cytotoxic anthracycline antibiotic obtained from Streptomyces peucetius var. caesius. The exact mechanism of the antitumour activity of doxorubicin is not known. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic effects. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix thus preventing their unwinding for replication.

Pharmacokinetics Properties

Doxorubicin is a long-circulating pegylated liposomal formulation of doxorubicin hydrochloride. Pegylated liposomes contain surface-grafted segments of the hydrophilic polymer methoxypolyethylene glycol (MPEG). These linear MPEG groups extend from the liposome surface creating a protective coating that reduces interactions between the lipid bilayer membrane and the plasma components. This allows the doxorubicin liposomes to circulate for prolonged periods in the blood stream. Pegylated liposomes are small enough (average diameter of approximately 100 nm) to pass intact (extravasate) through defective blood vessels supplying tumours. Evidence of penetration of pegylated liposomes from blood vessels and their entry and accumulation in tumours has been seen in mice with C-26 colon carcinoma tumours and in transgenic mice with KS-like lesions. The pegylated liposomes also have a low permeability lipid matrix and internal aqueous buffer system that combine to keep doxorubicin hydrochloride encapsulated during liposome residence time in circulation.

The plasma pharmacokinetics of doxorubicin in humans differ significantly from those reported in the literature for standard doxorubicin hydrochloride preparations. At lower doses (10 mg/m^2–20 mg/m^2) doxorubicin displayed linear pharmacokinetics. Over the dose range of 10 mg/m^2–60 mg/m^2 doxorubicin displayed non-linear pharmacokinetics. Standard doxorubicin hydrochloride displays extensive tissue distribution (volume of distribution: 700 to 1,100 l/m^2) and a rapid elimination clearance (24 to 73 l/h/m^2). In contrast, the pharmacokinetic profile of doxorubicin indicates that doxorubicin is confined mostly to the vascular fluid volume and that the clearance of doxorubicin from the blood is dependent upon the liposomal carrier. Doxorubicin becomes available after the liposomes are extravasated and enter the tissue compartment.

At equivalent doses, the plasma concentration and AUC values of doxorubicin which represent mostly pegylated liposomal doxorubicin hydrochloride (containing 90% to 95% of the measured

doxorubicin) are significantly higher than those achieved with standard doxorubicin hydrochloride preparations.

Doxorubicin should not be used interchangeably with other formulations of doxorubicin hydrochloride.

11. PHARMACEUTICAL INFORMATION

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section Special precautions for disposal and other handling.

Shelf Life

Unopened vial: 18 Months

After Dilution: Doxorubicin Hydrochloride liposomal Injection after dilution with 5% Dextrose Injection may be stored up to 36 hours at 2°C-8°C and upto 3 hours at 25°C

Precautions for Storage

Store in refrigerator, 2°C-8°C

Do not freeze

Retain vial in container until time of use.

Nature and contents of container

The product is packed in USP Type-I clear glass vial stoppered with 20 mm ready to sterilize grey bromobutyl rubber stopper and sealed with 20 mm flip-off seal.

Dosage Form and Pack Sizes:

Concentrate for Solution for Infusion

Pack Size: 1 vial in a carton

Packaging available:

10ml, 25 ml

Special precautions for disposal and other handling

General precautions

Do not use material that shows evidence of precipitation or any other particulate matter.

Caution must be exercised in handling doxorubicin solution. The use of gloves is required. If Doxorubicin comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. Doxorubicin must be handled and disposed of in a manner consistent with that of other anticancer medicinal products in accordance with local requirements.

Determine the dose of doxorubicin to be administered (based upon the recommended dose and the patient's body surface area). Take the appropriate volume of doxorubicin up into a sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in doxorubicin. The appropriate dose of doxorubicin must be diluted in 5% (50 mg/ml) glucose solution for infusion prior to administration. For doses < 90 mg, dilute doxorubicin in 250 ml, and

for doses ≥ 90 mg, dilute doxorubicin in 500 ml. This can be infused over 60 or 90 minutes as detailed in posology and method of administration.

The use of any diluent other than 5% (50 mg/ml) glucose solution for infusion, or the presence of any bacteriostatic agent such as benzyl alcohol may cause precipitation of doxorubicin.

It is recommended that the doxorubicin infusion line be connected through the side port of an intravenous infusion of 5% (50 mg/ml) glucose. Infusion may be given through a peripheral vein. Do not use with in-line filters.

Manufactured for Dr. Reddy's Laboratories Limited at:

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