PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

DOXOCCORD LP (Pegylated Liposomal Doxorubicin Hydrochloride Concentrate for Solution for Infusion 2mg/ml (10 ml & 25 ml Vial)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Doxorubicin Hydrochloride Ph.Eur. 2 mg

Excipients with known effect
Contains fully hydrogenated soy phosphatidylcholine (from soyabean) - see section *4.3 Contraindications*

For the full list of excipients, *see section 6.1.*

3. PHARMACEUTICAL FORM

DOXOCCORD LP is pegylated liposomal formulation of doxorubicin hydrochloride.

The drug product is a translucent red coloured dispersion filled in a clear glass vial. When examined under suitable conditions of visibility it should be practically free from particles.
After dilution: A red coloured solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Doxoccord LP 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/mm^3) and extensive mucocutaneous or visceral disease.

Doxoccord LP 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).

4.2 Posology and method of administration

Doxoccord LP should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic agents.
Doxoccord LP exhibits unique pharmacokinetic properties and must not be used interchangeably with other formulations of doxorubicin hydrochloride.

Posology

Breast cancer/Ovarian cancer

Doxoccord LP 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

Doxoccord LP 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

Doxoccord LP 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 Doxoccord LP 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 Doxoccord LP 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 provided in following Table 4.

Table 1. Palmar–Plantar erythrodysesthesia

	Week after prior Doxoccord LP dose		
Toxicity grade at current assessment	**Week 4**	**Week 5**	**Week 6**
Grade 1	**Redose unless** patient has experienced a previous grade 3 or 4 skin	**Redose unless** patient has experienced a previous grade 3 or 4 skin	**Decrease dose by 25%; return to 4 week interval**

(mild erythema, swelling, or desquamation not interfering with daily activities)	toxicity, in which case wait an additional week	toxicity, in which case wait an additional week	
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 Doxoccord LP**
Grade 4 (diffuse or local process causing infectious complications, or a bedridden state or hospitalisation)	**Wait an additional week**	**Wait an additional week**	**Discontinue Doxoccord LP**

Table 2. Stomatitis

	Week after prior Doxoccord LP 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 Doxoccord LP**
Grade 4 (requires parenteral or enteral support)	**Wait an additional week**	**Wait an additional week**	**Discontinue Doxoccord LP**

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 Doxoccord LP in combination with bortezomib who experience PPE or stomatitis, the Doxoccord LP 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 Doxoccord LP + bortezomib combination therapy - patients with multiple myeloma

Patient status	**Doxoccord LP**	**Bortezomib**
Fever ≥ 38°C and ANC < 1,000/mm³	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/mm³ Haemoglobin < 8 g/dl ANC < 500/mm³	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 haematologic 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-haematologic 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/m^2 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 Doxoccord LP.

Patients with impaired renal function

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

Hepatic impairment

Doxoccord LP 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 Doxoccord LP 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. Doxoccord LP 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 Doxoccord LP 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 Doxoccord LP in patients with splenectomy, treatment with Doxoccord LP is not recommended.

Method of administration
For doses < 90 mg: dilute Doxoccord LP in 250 ml Dextrose 5% in water.
For doses ≥ 90 mg: dilute Doxoccord LP 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 Doxoccord LP 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. Doxoccord LP 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 Doxoccord LP 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 Doxoccord LP infusions may be administered over a 60 minute period.

Multiple myeloma
The intravenous catheter and tubing should be flushed with Dextrose 5% in water between administration of Doxoccord LP 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 Doxoccord LP 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 Doxoccord LP will be administered over 1 hour, as tolerated. If an infusion reaction to Doxoccord LP occurs, stop the infusion and after the symptoms resolve, attempt to administer the remaining Doxoccord LP 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
Doxoccord LP, diluted in 250 ml Dextrose 5% in water, is administered by intravenous infusion over 30 minutes.

Route of Administration
Intravenous

4.3 Contraindications

Hypersensitivity to the active substance, peanut or soya, or to any of the excipients.
Doxoccord LP must not be used to treat AIDS-KS that may be treated effectively with local therapy or systemic alfa-interferon.

4.4 Special warnings and precautions for use

Given the difference in pharmacokinetic profiles and dosing schedules, Doxoccord LP should not be used interchangeably with other formulations of doxorubicin hydrochloride.
Cardiac toxicity
It is recommended that all patients receiving Doxoccord LP 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 Doxoccord LP 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 Doxoccord LP therapy and repeated periodically during treatment. The evaluation of left ventricular function is considered to be mandatory before each additional administration of Doxoccord LP 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 Doxoccord LP therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.
In patients with cardiac disease requiring treatment, administer Doxoccord LP only when the benefit outweighs the risk to the patient.
Exercise caution in patients with impaired cardiac function who receive Doxoccord LP. 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.

Myelosuppression
Many patients treated with pegylated liposomal doxorubicin hydrochloride 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 pegylated liposomal doxorubicin hydrochloride therapy, and at a minimum, prior to each dose of pegylated liposomal doxorubicin hydrochloride.
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 pegylated liposomal doxorubicin hydrochloride. 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 pegylated liposomal doxorubicin hydrochloride.
Therefore, any patient treated with pegylated liposomal doxorubicin hydrochloride 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 pegylated liposomal doxorubicin hydrochloride or those receiving a cumulative pegylated liposomal doxorubicin hydrochloride dose greater than 720 mg/m^2. Cases of secondary oral cancer were diagnosed both, during treatment with pegylated liposomal doxorubicin hydrochloride, 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 pegylated liposomal doxorubicin hydrochloride. 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 Doxoccord LP contains sucrose and the dose is administered in Dextrose 5% in water.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per dose and is essentially 'sodium-free'.

For common adverse reaction which required dose modification or discontinuation see *section 4.8 Undesirable effects.*

4.5 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. Pegylated liposomal doxorubicin hydrochloride, 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.

4.6 Fertility, pregnancy and lactation

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

Women of child-bearing potential/contraception in men and women
Due to the genotoxic potential of pegylated liposomal doxorubicin hydrochloride, women of child-bearing potential should use effective contraceptive measures while being treated with pegylated liposomal doxorubicin hydrochloride and for 8 months following completion of treatment.
Men are recommended to use effective contraceptive measures and to not father a child while receiving pegylated liposomal doxorubicin hydrochloride and for 6 months following completion of treatment.

Breast-feeding
It is not known whether pegylated liposomal doxorubicin hydrochloride 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 pegylated liposomal doxorubicin hydrochloride 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 pegylated liposomal doxorubicin hydrochloride on human fertility has not been evaluated.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most frequent adverse reactions ≥20%) were neutropaenia, nausea, leukopaenia, anaemia, and fatigue.

Severe adverse reactions (Grade 3/4 adverse reactions occurring in ≥2% of patients) were neutropaenia, PPE, leukopaenia, lymphopaenia, anaemia, thrombocytopaenia, stomatitis, fatigue, diarrhoea, vomiting, nausea, pyrexia, dyspnoea, and pneumonia. Less frequently reported severe

adverse reactions included Pneumocystis jirovecii pneumonia, abdominal pain, cytomegalovirus infection including cytomegalovirus chorioretinitis, asthenia, cardiac arrest, cardiac failure, cardiac failure congestive, pulmonary embolism, thrombophlebitis, venous thrombosis, anaphylactic reaction, anaphylactoid reaction, toxic epidermal necrolysis, and Stevens-Johnson syndrome.

Tabulated list of adverse reactions

Table 5 summarises the adverse drug reactions that occurred in patients receiving pegylated liposomal doxorubicin hydrochloride in 4,231 patients for the treatment of breast cancer, ovarian cancer, multiple myeloma, and AIDS-related KS. Post-marketing adverse reactions are also included, as indicated by "b". Frequencies are defined as very common (≥1/10), common ≥1/100 to < 1/10), uncommon ≥1/1,000 to < 1/100), rare ≥1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness

Table 5: Adverse reactions in patients treated with pegylated liposomal doxorubicin hydrochloride

System Organ Class	**Frequency all grades**	**Adverse drug reaction**
Infections and infestations	Common	Sepsis
		Pneumonia
		Pneumocystis jirovecii pneumonia
		Cytomegalovirus infection including cytomegalovirus chorioretinitis
		Mycobacterium avium complex infection
		Candidiasis
		Herpes zoster
		Urinary tract infection
		Infection
		Upper respiratory tract infection
		Oral candidiasis
		Folliculitis
		Pharyngitis
		Nasopharyngitis
	Uncommon	Herpes simplex
		Fungal infection
	Rare	Opportunistic infection (including *Aspergillus, Histoplasma*, *Isospora*, *Legionella*, *Microsporidium*, *Salmonella*, *Staphylococcus*, *Toxoplasma*, *Tuberculosis*)[a]
Neoplasms benign,	Not known	Acute myeloid leukaemia[b]
		Myelodysplastic syndrome[b]

malignant and unspecified (including cysts and polyps)		Oral neoplasm[b]
Blood and lymphatic system disorders	Very common	Leukopaenia
		Neutropaenia
		Lymphopaenia
		Anaemia (including hypochromic)
	Common	Thrombocytopaenia
		Febrile neutropaenia
	Uncommon	Pancytopaenia
		Thrombocytosis
	Rare	Bone marrow failure
Immune system disorders	Uncommon	Hypersensitivity
		Anaphylactic reaction
	Rare	Anaphylactoid reaction
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Cachexia
		Dehydration
		Hypokalaemia
		Hyponatraemia
		Hypocalcaemia
	Uncommon	Hyperkalaemia
		Hypomagnesaemia
Psychiatric disorders	Common	Confusional state
		Anxiety
		Depression
		Insomnia
Nervous system disorders	Common	Neuropathy peripheral
		Peripheral sensory neuropathy
		Neuralgia
		Paraesthesia
		Hypoaesthesia
		Dysgeusia
		Headache
		Lethargy
		Dizziness
	Uncommon	Polyneuropathy
		Convulsion
		Syncope
		Dysaesthesia
		Somnolence
Eye disorders	Common	Conjunctivitis
	Uncommon	Vision blurred
		Lacrimation increased
	Rare	Retinitis
Cardiac	Common	Tachycardia

disorders[a]	Uncommon	Palpitations
		Cardiac arrest
		Cardiac failure
		Cardiac failure congestive
		Cardiomyopathy
		Cardiotoxicity
	Rare	Ventricular arrhythmia
		Bundle branch block right
		Conduction disorder
		Atrioventricular block
		Cyanosis
Vascular disorders	Common	Hypertension
		Hypotension
		Flushing
	Uncommon	Pulmonary embolism
		Infusion site necrosis (including soft tissue necrosis and skin necrosis)
		Phlebitis
		Orthostatic hypotension
	Rare	Thrombophlebitis
		Venous thrombosis
		Vasodilatation
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
		Dyspnoea exertional
		Epistaxis
		Cough
	Uncommon	Asthma
		Chest discomfort
	Rare	Throat tightness
	Not known	Interstitial lung disease
Gastrointestinal disorders	Very common	Stomatitis
		Nausea
		Vomiting
		Diarrhoea
		Constipation
	Common	Gastritis
		Aphthous stomatitis
		Mouth ulceration
		Dyspepsia
		Dysphagia
		Oesophagitis
		Abdominal pain
		Abdominal pain upper
		Oral pain
		Dry mouth
	Uncommon	Flatulence
		Gingivitis
	Rare	Glossitis

		Lip ulceration
Skin and subcutaneous tissue disorders	Very common	Palmar plantar erythrodysaesthesia syndrome[a]
		Rash (including erythematous, maculo-papular, and papular)
		Alopecia
	Common	Skin exfoliation
		Blister
		Dry skin
		Erythema
		Pruritus
		Hyperhidrosis
		Skin hyperpigmentation
	Uncommon	Dermatitis
		Dermatitis exfoliative
		Acne
		Skin ulcer
		Dermatitis allergic
		Urticaria
		Skin discolouration
		Petechiae
		Pigmentation disorder
		Nail disorder
	Rare	Toxic epidermal necrolysis
		Erythema multiforme
		Dermatitis bullous
		Lichenoid keratosis
	Not known	Stevens-Johnson syndrome[b]
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain (including musculoskeletal chest pain, back pain, pain in extremity)
	Common	Muscle spasms
		Myalgia
		Arthralgia
		Bone pain
	Uncommon	Muscular weakness
Renal and urinary disorders	Common	Dysuria
Reproductive disorders	Uncommon	Breast pain
	Rare	Vaginal infection
		Scrotal erythema
General disorders and administration site conditions	Very common	Pyrexia
		Fatigue
	Common	Infusion-related reaction
		Pain
		Chest pain
		Influenza-like illness
		Chills
		Mucosal inflammation

		Asthenia
		Malaise
		Oedema
		Oedema peripheral
	Uncommon	Administration site extravasation
		Injection site reaction
		Face oedema
		Hyperthermia
	Rare	Mucous membrane disorder
Investigations	Common	Weight decreased
	Uncommon	Ejection fraction decreased
	Rare	Liver function test abnormal (including Blood bilirubin increased, Alanine aminotransferase increased and Aspartate aminotransferase increased)
		Blood creatinine increased
Injury, poisoning and procedural complications	Uncommon	Radiation recall phenomenon[a]

[a] See Description of selected adverse reactions
[b] Post-marketing adverse reaction

Description of selected adverse reactions

Palmar plantar erythrodysaesthesia
The most common undesirable effect reported in breast/ovarian clinical trials was palmar-plantar erythrodysesthesia (PPE). The overall incidence of PPE reported was 41.3% and 51.1% in the ovarian and breast clinical trials, respectively. These effects were mostly mild, with severe (grade 3) cases reported in 16.3% and 19.6% of patients. The reported incidence of life-threatening (grade 4) cases was < 1%. PPE infrequently resulted in permanent treatment discontinuation (1.9% and 10.8%). PPE was reported in 16% of multiple myeloma patients treated with pegylated liposomal doxorubicin hydrochloride plus bortezomib combination therapy. Grade 3 PPE was reported in 5% of patients. No grade 4 PPE was reported. The rate of PPE was substantially lower in the AIDS-KS population (1.3% all grade, 0.4% grade 3 PPE, no grade 4 PPE).

Opportunistic infections
Respiratory undesirable effects commonly occurred in clinical studies of pegylated liposomal doxorubicin hydrochloride and may be related to opportunistic infections (OI's) in the AIDS population. Opportunistic infections are observed in KS patients after administration with pegylated liposomal doxorubicin hydrochloride, and are frequently observed in patients with HIV induced immunodeficiency. The most frequently observed OI's in clinical studies were candidiasis, cytomegalovirus, herpes simplex, Pneumocystis jirovecii pneumonia, and mycobacterium avium complex.

Cardiac toxicity

An increased incidence of congestive heart failure is associated with pegylated liposomal doxorubicin hydrochloride therapy at cumulative lifetime doses > 450 mg/m^2 or at lower doses for patientswith cardiac risk factors.
Endomyocardial biopsies on nine of ten AIDS-KS patients receiving cumulative doses of pegylated liposomal doxorubicin hydrochloride greater than 460 mg/m^2 indicate no evidence of anthracycline-induced cardiomyopathy. The recommended dose of pegylated liposomal doxorubicin hydrochloride 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 pegylated liposomal doxorubicin hydrochloride 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.

In the pivotal phase III trial versus doxorubicin, 58/509 (11.4%) randomised subjects (10 treated with pegylated liposomal doxorubicin hydrochloride at a dose of 50 mg/m^2/every 4 weeks versus 48 treated with doxorubicin at a dose of 60 mg/m^2/every 3 weeks) met the protocol-defined criteria for cardiac toxicity during treatment and/or follow-up. 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). None of the 10 pegylated liposomal doxorubicin hydrochloride subjects who had cardiac toxicity by LVEF criteria developed signs and symptoms of CHF. In contrast, 10 of 48 doxorubicin subjects who had cardiac toxicity by LVEF criteria also developed signs and symptoms of CHF.

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. Of the 418 patients treated with pegylated liposomal doxorubicin hydrochloride 50 mg/m^2/cycle, and having a baseline measurement of left ventricular ejection fraction (LVEF) and at least one follow-up measurement assessed by MUGA scan, 88 patients had a cumulative anthracycline dose of > 400 mg/m^2, an exposure level associated with an increased risk of cardiovascular toxicity with conventional doxorubicin. Only 13 of these 88 patients (15%) had at least one clinically significant change in their LVEF, defined as an LVEF value less than 45% or a decrease of at least 20 points from baseline. Furthermore, only 1 patient (cumulative anthracycline dose of 944 mg/m^2), discontinued study treatment because of clinical symptoms of congestive heart failure.

Radiation recall phenomenon
Recall of skin reaction due to prior radiotherapy has occurred uncommonly with pegylated liposomal doxorubicin hydrochloride administration.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances).
Mechanism of action
The active ingredient of Doxoccord LP 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.

5.2 Pharmacokinetic properties

Doxoccord LP 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 pegylated liposomal doxorubicin hydrochloride 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 pegylated liposomal doxorubicin hydrochloride 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) pegylated liposomal doxorubicin hydrochloride displayed linear pharmacokinetics. Over the dose range of 10 mg/m^2–60 mg/m^2 pegylated liposomal doxorubicin hydrochloride 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 pegylated liposomal doxorubicin hydrochloride indicates that pegylated liposomal doxorubicin hydrochloride 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 pegylated liposomal doxorubicin hydrochloride 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. Pegylated liposomal doxorubicin hydrochloride should not be used interchangeably with other formulations of doxorubicin hydrochloride.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- N-(carbonyl-methoxypolyethylene glycol-2000)-1,2-distearoyl- sn-glycero-3-phosphoethanolamine, sodium salt (MPEG 2000-DSPE)
- Hydrogenated soy phosphatidylcholine
- Cholesterol
- Ammonium sulphate
- Sucrose
- Histidine
- Hydrochloric acid concentrated (for pH adjustment)
- Sodium hydroxide (for pH adjustment)
- Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in *section 6.6 Special precautions for disposal and other handling*.

6.3 Shelf life

12 months.

After dilution:

- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.

- From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C.

- Partially used vials must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

For storage conditions of the diluted medicinal product, see section *6.3 Shelf life*.

6.5 Nature and contents of container

Type I glass vials, each with a siliconised grey bromobutyl stopper, and an aluminium seal, with a deliverable volume of 10 ml (20 mg) or 25 ml (50 mg).

Pegylated liposomal doxorubicin is supplied as a single pack of one vial.

6.6 Special precautions for disposal and other handling

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

Caution must be exercised in handling Doxoccord LP solution. The use of gloves is required. If Doxoccord LP comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. Doxoccord LP 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 Doxoccord LP to be administered (based upon the recommended dose and the patient's body surface area). Take the appropriate volume of Doxoccord LP up into a sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Doxoccord LP.

The appropriate dose of Doxoccord LP must be diluted in Dextrose 5% in water prior to administration. For doses < 90 mg, dilute Doxoccord LP in 250 ml, and for doses ≥ 90 mg, dilute Doxoccord LP 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 Dextrose 5% in water, or the presence of any bacteriostatic agent such as benzyl alcohol may cause precipitation of Doxoccord LP.

It is recommended that the Doxoccord LP infusion line be connected through the side port of an intravenous infusion of Dextrose 5% in water. Infusion may be given through a peripheral vein. Do not use with in-line filters.

7. MARKETING AUTHORISATION HOLDER

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8. DATE OF REVISION OF THE TEXT

November 2025