Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

DaunoXome 2 mg/mL concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Daunorubicin present as citrate salt; equivalent to daunorubicin base, 2 mg/ml, encapsulated in liposomes.

Each single dose vial of DaunoXome contains 50 mg daunorubicin.

For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Each vial contains a translucent red liposomal dispersion free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

AIDS-related Kaposi's Sarcoma in patients with low CD4 cell counts (<200cells/mm^3) and extensive mucocutaneous or visceral disease.

DaunoXome should not be used to treat AIDS-related KS that may be effectively treated with local therapy.

4.2 Posology and method of administration

DaunoXome should be administered by intravenous infusion. The recommended initial dose of DaunoXome in patients with AIDS-related Kaposi's sarcoma is 40 mg/m^2 every two weeks. The dosage of DaunoXome must be adjusted for each patient. Therapy should be continued as long as disease control can be maintained.

DaunoXome should be diluted with 5% dextrose for infusion before administration. The recommended concentration after dilution is between 0.2 mg and 1 mg daunorubicin/ml of solution. DaunoXome should be administered intravenously over a minimum period of 30-60 minutes *(see also Sections 6.2, 6.3 and 6.6.).*

DaunoXome must not be given by the intramuscular or subcutaneous route or as a bolus injection.

DaunoXome is a liposomal preparation and should not be used interchangeably with conventional daunorubicin.

Pediatric patients: DaunoXome is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Elderly: The safety and effectiveness of DaunoXome in patients over 65 years of age have not been established. Cardiotoxicity may be more frequent in the elderly *(see Section 4.4).*

Hepatic impairment and renal impairment:
DaunoXome has not been studied in patients with impaired liver or renal function, therefore DaunoXome is not recommended in such situations.

4.3 Contraindications

Hypersensitivity to DaunoXome, any of its excipients or other anthracyclines /anthracenediones.

Breast feeding.

4.4 Special warnings and precautions for use

The decision to treat must be based on an evaluation, by the physician, of the benefits and risks for the individual patient.

Cardiotoxicity

DaunoXome and other anthracyclines can cause cardiotoxicity, notably congestive heart failure due to cardiomyopathy. The onset of symptoms can be sudden and may not occur until weeks or months after discontinuation of therapy. Cardiac damage may be irreversible and there have been rare reports of fatalities, usually in patients with risk factors.

The risk of cardiotoxicity increases with total cumulative dosage of anthracyclines. Caution must therefore be exercised in patients previously treated with anthracyclines, or those with previous (or concomitant) therapy with other cardiotoxic compounds such as 5-fluorouracil (5-FU).

The maximum cumulative dose of DaunoXome is not known. The pharmacokinetics of liposomal (DaunoXome) and conventional daunorubicin are different. However, based on experience with conventional daunorubicin, daunorubicin hydrochloride must not be used if the maximum cumulative dose of daunorubicin hydrochloride, 500-600 mg/m^2 in adults, or the maximum cumulative dose of other cardiotoxic anthracyclines (e.g. idarubicin, epirubicin) or anthracenediones (e.g. mitoxantrone), has been previously administered, as the risk of life-threatening cardiac damage markedly increases. The total cumulative dose should be limited to 400 mg/m^2 in patients who have had previous radiation therapy to the chest or previous administration (at less than the maximum cumulative dose) of other potentially cardiotoxic drugs.

The risk of cardiotoxicity appears to be higher in those with pre-existing cardiovascular disease, a history of mediastinal radiation and the elderly. Caution must therefore be exercised when DaunoXome is given to these patients. DaunoXome should only be given to patients with cardiovascular disease when the benefit outweighs the risks.

Experience in patients treated with high dose DaunoXome (above 60 mg/m^2) for malignancies other than Kaposi's sarcoma indicates that the risk of cardiotoxicity may be higher in these patients.

Cardiac monitoring

Careful monitoring of cardiac function is essential in patients treated with DaunoXome.

Cardiomyopathy induced by anthracyclines is usually associated with a decreased left ventricular ejection fraction (LVEF) measured by echocardiography or by MUGA (Multiple Gated Acquisition) scan. Measurement of LVEF provides a more specific method for monitoring cardiac function than ECG.

All patients should undergo baseline ECGs, echocardiography and measurement of LVEF prior to starting DaunoXome. These tests should be repeated regularly during treatment. Furthermore, in all patients, LVEF must be determined when a cumulative dose of 320 mg/m^2 has been reached, then every 160 mg/m^2 thereafter, in order to identify at an early stage any changes in LVEF that may be a precursor to cardiomyopathy if DaunoXome therapy is continued.

In patients with risk factors for cardiotoxicity with DaunoXome, or those receiving high dose DaunoXome per cycle (e.g. 120 mg/m^2 or above), decreases in cardiac function may occur at lower cumulative doses of DaunoXome, therefore consideration should be given to determination of LVEF after each treatment cycle and before any additional DaunoXome is administered.

Transient ECG changes such as T-wave flattening, S-T segment depression and benign arrhythmias are not considered mandatory indications for cessation of DaunoXome. A reduction of the QRS wave is considered more indicative of cardiac toxicity.

Whenever cardiomyopathy is suspected, and/or LVEF has decreased significantly as compared to pre-treatment values (e.g. 20% decline) and/or if the LVEF is lower than would be expected (e.g. <45%), the benefit of continued therapy must be carefully weighed against the risk of producing irreversible cardiac damage.

It is recommended that treatment with DaunoXome is stopped if clinical signs of cardiotoxicity appear.

Several long-term studies in children also suggest that after anthracycline treatment congestive cardiomyopathies with a latency of many years may occur.

Haematological toxicity

DaunoXome is a bone marrow suppressant. The most significant effect is usually neutropenia, which may be severe and result in fever and infection. Anemia and thrombocytopenia may also occur, but are usually less marked. Persistent severe myelosuppression may result in sepsis, or haemorrhage. Complete blood counts must be performed prior to each dose and monitored, as medically appropriate, during the course of DaunoXome therapy.

Patients must be observed carefully for evidence of intercurrent or opportunistic infections.

Haematological toxicity may require dose reduction of DaunoXome or suspension or delay of therapy. The colony stimulating factor GCSF has been used to manage patients with neutropenia.

Caution is warranted when combining DaunoXome with other agents which suppress bone marrow function.

Injection site reactions

Care should be taken to ensure that there is no extravasation of DaunoXome during administration. Paravenous administration has resulted in erythema, pain and swelling around the site of tissue infiltration. These changes are generally transitory, resolving within 6 months. However, localised tissue necrosis must still be regarded as a possible consequence of extravasation.

If any signs or symptoms of extravasation occur (e.g. stinging, erythema), the infusion should be stopped immediately and re-started in another vein. It may be inappropriate to provide any measure that might cause release of the drug from the liposome (such as application of ice or corticosteroids, instillation of local antidotes, local compression, etc.)

Acute infusion-associated reactions

Acute infusion-related reactions have been reported in patients treated with DaunoXome. Symptoms typically include back pain, flushing, chest tightness and dyspnoea. These infusion reactions may occur during the patient's first exposure to DaunoXome, or during re-exposure in a patient who had previously received DaunoXome without incident. Infusion-related reactions generally occur within the first 10 minutes of the infusion and subside when the infusion is slowed or halted. Acute allergic/anaphylactic reactions, sometimes associated with hypotension, have also been reported.

Caution should be exercised when DaunoXome is used concomitantly with other myelosuppressive or cardiotoxic agents *(see Section 4.5).* Caution is also required with preceding, concurrent or planned radiotherapy as these patients, during treatment with daunorubicin hydrochloride, have an increased risk of local reactions in the radiation area (recall phenomena).

Liver and renal function

Daunorubicin hydrochloride is metabolised predominantly in the liver and is excreted via the bile. Monitoring of liver and renal function before starting and during treatment with DaunoXome, is recommended. DaunoXome is not recommended in patients with liver or renal impairment, see Section 4.2.

Immunosuppressant effects/increased susceptibility to infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including daunorubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving daunorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Reproductive system and breast disorders

Daunorubicin hydrochloride inhibits fertility. Based on experience with conventional daunorubicin, amenorrhoea and azoospermia may occur. Irreversible disorders of fertility are possible (see Section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Daunorubicin hydrochloride is mainly metabolised in the liver; concomitant medication influencing liver function may also therefore influence the metabolism or pharmacokinetics of daunorubicin hydrochloride and, as a consequence, influence efficacy and/or toxicity.

Protease Inhibitors (PIs) and Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are known inhibitors of Cytochrome P450 IIIA (CYP-3A) and may also have a role in the inhibition of the drug transporting protein, P-glycoprotein (P-gp). Daunorubicin and other anthracyclines may undergo some metabolism by CYP-3A and are known substrates of P-gp. There is therefore a theoretical possibility of interaction between DaunoXome and these two groups of antiviral therapy. To date however, a single study has indicated that there is no effect of PIs or NNRTIs on DaunoXome's pharmacokinetic properties. Limited data from one small study where patients were treated with and without protease inhibitors indicate that there were no major changes in DaunoXome associated toxicity.

Caution should be exercised when DaunoXome is used concomitantly with other myelosuppressive or cardiotoxic agents. The risk of gastrointestinal side-effects increases with the concurrent administration of other cytotoxics. Mucositis (oral and gastrointestinal) occurring in association with daunorubicin-containing chemotherapy may impair the absorption of oral medicinal products. Live vaccines should be avoided. Killed or inactivated vaccines should be used with caution (see Section 4.4).

Caution should be taken when DaunoXome is administered concurrently with antiplatelet drugs such as aspirin (acetylsalicylic acid), clopidogrel, dipyridamole, eptifibatide and other agents which inhibit platelet/thrombocyte aggregation. Thrombocytopenic patients will be at increased risk of bleeding disorders.

4.6 Fertility, pregnancy and lactation

Fertility and Contraceptive Measures
Daunorubicin could induce chromosomal damage in human spermatozoa. Men should receive counselling on sperm cryopreservation before the start of daunorubicin treatment because of the possibility of irreversible infertility. Men undergoing treatment with daunorubicin should use effective contraceptive methods during and for 6 months after treatment.

Women of childbearing potential have to use effective contraception while they or their male partner is receiving DaunoXome, and for 6 months following discontinuation of treatment with DaunoXome. For women who want to become pregnant after completing DaunoXome treatment, genetic counselling is also recommended.

Pregnancy
Studies in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data). Like most other

anticancer drugs, daunorubicin has shown embryotoxic, teratogenic, mutagenic and carcinogenic potential in animals. There are no or limited amount of data from the use of daunorubicin in pregnant women, although a few women who received daunorubicin during the second and third trimesters of pregnancy have delivered apparently normal infants.

According to experimental data, the drug must be considered as a potential cause of foetal malformations when administered to a pregnant woman. Daunorubicin should not be used during pregnancy unless the clinical condition of the woman requires treatment with daunorubicin and justifies the potential risk to the foetus. Women of child-bearing potential who have to undergo daunorubicin therapy should be informed about the potential hazard to the foetus and should be advised to avoid becoming pregnant during treatment. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the woman should be informed of the potential hazard to the foetus. The possibility of genetic counselling should also be utilised. In any case, cardiologic examination and a blood count are recommended in foetuses and newborns born to mothers who received treatment with daunorubicin during pregnancy.

Lactation
It is unknown whether daunorubicin/metabolites are excreted in human milk; other anthracyclines are excreted in breast milk. DaunoXome is contraindicated during breast-feeding (see Section 4.3 Contraindications).

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of DaunoXome on the ability to drive and use machines. However, patients should be informed that dizziness has been reported during treatment with DaunoXome.

4.8 Undesirable effects

The adverse reactions considered at least possibly related to treatment with DaunoXome are listed below, by body system organ class and absolute frequency. Frequencies are defined as follows: very common ≥ 10%; common ≥ 1% and < 10%; uncommon ≥ 0.1% and < 1%; rare ≥ 0.01% and < 0.1%, very rare <0.01%, not known (cannot be estimated from the available data).

System Organ Class	**Frequency of adverse reactions**				
	Very Common	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations	Infections		Sepsis Septic shock*		
Blood and lymphatic system disorders	Bone marrow suppression, Agranulocytosis, Neutropenia, Febrile neutropenia, Leucopenia, Pancytopenia, Thrombocytopenia and Anemia*				
Immune system disorders	Allergic reactions			Anaphylactic reaction	
Metabolism and nutritional disorders		Dehydration			
Psychiatric disorders		Depression			

Nervous system disorders	Headache	Dizziness			
Cardiac disorders*		Decreased left ventricular ejection fraction	Congestive heart failure, Cardiomyopathy	Atrial fibrillation, Myocardial infarction	
Vascular disorders	Haemorrhage				Shock
Respiratory, thoracic and mediastinal disorders	Dyspnoea				
Gastrointestinal disorders	Stomatitis, Mucous ulcerations, Nausea, Vomiting, Diarrhoea, Abdominal pain				
Hepatobiliary disorders					Transient elevations in serum bilirubin, aspartate aminotransfer-ase (AST) and alkaline phosphatase (ALP) concentrations Hepatitis, Hepatic failure
Skin and subcutaneous tissue disorders	Alopecia			Palmar-plantar erythrodysaes-thesia syndrome**	
Renal and urinary disorders					Red discolouration of urine
Reproductive system and breast disorders					Amenorrhoea, Azoospermia
General disorders and administration site conditions	Infusion-associated reactions (including back pain, flushing, chest tightness,	Extravasation at the injection site may result in erythema, pain and			

	and dyspnoea)*, Asthenia, Fatigue, Fever, Chills	swelling *			

* See Section 4.4
** Palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) has been reported rarely in patients treated with high dose DaunoXome and cytarabine for leukaemia. The condition is characterised by swelling, pain, tingling and erythema of the palms and soles, which may lead to desquamation of the skin in some patients. Dose reduction or delayed dosing may be required to manage the condition.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

From experience with non-liposomal anthracyclin preparations, the primary anticipated toxicity from such an overdose would be myelosuppression. Furthermore other side effects may occur in more pronounced form, like cardiomyopathy. In the event of overdose bone marrow function and cardiac function should be carefully monitored with appropriate therapy for any severe side−effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code L01DB02, Pharmacotherapeutic group: Antineoplastic agent

The active ingredient of DaunoXome is daunorubicin, a cytotoxic anthracycline antibiotic isolated from Streptomyces coeruleorubidus. The exact mechanism of the antitumour activity of daunorubicin 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. Daunorubicin also has antibacterial and immunosuppressive properties.

DaunoXome is a liposomal preparation of daunorubicin formulated to prolong circulation time and to maximise the selectivity of daunorubicin for tumors. While in the circulation, the DaunoXome formulation helps to protect the entrapped daunorubicin from chemical and enzymatic degradation, minimises protein binding, and generally decreases uptake by normal (non-reticuloendothelial system) tissues.

Tumour selectivity of DaunoXome has been demonstrated for transplanted tumours in animal models. The exact mechanism by which DaunoXome is able to deliver daunorubicin to solid tumours in situ is not known. However, it is believed to be a function of increased permeability of the tumour neovasculature to some particulates in the size range of DaunoXome. Once within the tumour environment, DaunoXome vesicles enter the tumour cells intact, after which liposomal disruption occurs with intracellular release of free daunorubicin. Pharmacokinetic studies also show measurable levels of free daunorubicin in plasma, which may have an additional anti-tumour effect. Results from *in vivo* therapeutic studies in mice, i.e., antitumour activity measured as increased median survival time and by reduced tumour size, have shown that DaunoXome has improved efficacy compared with daunorubicin at optimal doses. Clinical trials comparing liposomal and conventional daunorubicin have not been conducted.

5.2 Pharmacokinetic properties

Following the administration of DaunoXome, daunorubicin is present in plasma bound to liposomes and as free (protein-bound and non-protein-bound) drug.

The pharmacokinetic data of free daunorubicin is sparse and also somewhat deficient as analytical methods could not distinguish between daunorubicin and daunorubicinol. Following administration of conventional daunorubicin (80 mg/m^2) as an intravenous bolus, plasma levels were approximately 0.4±0.6 µg/ml after 15 minutes. The levels fell below 0.1 µg/ml within approximately 24-36 hours. The volume of distribution was 1055±235 l; daunorubicin exhibits extensive tissue binding. Clearance was approximately 223 ml/min, AUC approximately 10.3 µg.hr/ml. The plasma concentration-time curve shows a biphasic process; the slow elimination is probably due to slow release from the tissue binding sites. A small amount was excreted through the urine; Daunorubicin is probably largely excreted through a biliary pathway.

DaunoXome was administered as an intravenous infusion over 30 minutes in doses from 10 to 80 mg/m^2. The increase in AUC of total daunorubicin levels was somewhat greater than proportional to dose. Average maximum levels of total daunorubicin following 40 mg/m^2 were 18 µg/ml (range 15-22 µg/ml). Clearance for total levels was approximately 10 ml/min (range 7-15). The steady-state volume of distribution was around 4 l (range 2-6 l). Mean terminal half-life was 4 hours (range 3-6 hours). Maximum daunorubicinol levels were below 0.3 µg/ml following the IV administration of 40 mg/m^2 DaunoXome.

The exposure, expressed as the AUC of total daunorubicin levels, following administration of 80 mg/m^2 as DaunoXome was approximately 36-fold increased as compared with the AUC after administration of 80 mg/m^2 as conventional daunorubicin.

5.3 Preclinical safety data

Daunorubicin is mutagenic both *in vitro* and *in vivo*, and carcinogenic *in vivo*. A high incidence of mammary tumours was observed in rats treated with daunorubicin. Although no such studies have been conducted with DaunoXome, it is most likely that DaunoXome will have a similar mutagenic potential.

In experiments in rats, DaunoXome and daunorubicin have shown some renal toxicity; however, renal damage is not documented in the clinical use of daunorubicin. In experiments with mice, a cardiotoxic effect of DaunoXome was documented; in clinical practice however DaunoXome has so far proven less cardiotoxic than daunorubicin.

In mice, single IV doses of DaunoXome did not increase the myelosuppressive activity compared with equivalent doses of free daunorubicin.

Studies to evaluate the effects of liposomal daunorubicin on fertility have not been performed; however, the active ingredient, daunorubicin, caused testicular atrophy and total aplasia of spermatocytes in the seminiferous tubules in male dogs administered 0.25 mg/kg per day (approximately eight times the recommended human dose on a mg/m2 basis).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

List of excipients

Liposome:
Colfosceril stearate
Cholesterol
Citric acid

Buffer:
Sucrose
Glycine
Calcium chloride dihydrate

Hydrochloric acid
Sodium hydroxide
Water for injection

6.2 Incompatibilities

DaunoXome may only be mixed with 5% dextrose for infusion. If DaunoXome is mixed with saline, aggregation of the liposomes may result. Admixtures containing bacteriostatic agents such as benzyl alcohol or other detergent−like molecules should be avoided as well because such compounds can rupture the bilayer wall of the liposomes causing premature leakage of the active drug.

No incompatibilities of DaunoXome with other drugs have been reported. However, it is known that the active component daunorubicin is physically incompatible with heparin sodium and with dexamethasone phosphate when directly admixed. A precipitate is produced with either drug. Additionally, because of the chemical instability of the glycosidic bond of daunorubicin, admixture into a highly alkaline media (pH > 8.0) is not recommended.

6.3 Shelf life

The shelf life is 12 months when stored at 2−8º C.

Chemical and physical in-use stability has been demonstrated for DaunoXome diluted with 5% dextrose, see table below for details.

From a microbial point of view, diluted DaunoXome 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 2-8ºC for the 5% dextrose dilutions. This recommendation is made on the assumption that dilution has taken place in controlled and validated aseptic conditions.

Diluent	Dilution Ratio, mL to mL	Final Concentration Daunorubicin mg/mL	Duration of Chemical Stability at 25ºC
5% Dextrose	1:2	1.0	24 hours
	1:4	0.5	24 hours
	1:8	0.25	6 hours
	1:10	0.2	not recommended

6.4 Special precautions for storage

Store concentrate in a refrigerator (at 2−8º C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

DaunoXome is presented in 50−ml sterile Type 1glass Ph. Eur. vial. Each vial contains 25 ml liquid for infusion. The closure consists of a butyl rubber stopper and aluminum ring seal fitted with a removable plastic cap. Each single−dose vial is packed in a white chipboard carton. Included in each carton are directions for use.

Pack size 1 x 25 mL.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Do not store partially used vials for future patient use. Vials are for single use only. Discard any unused product. Visually examine the vial for evidence of deterioration. Evidence of deterioration include precipitation or crystals forming in the product, change in color from other than a translucent red color. If the vial shows evidence of damage including leakage or deterioration, do not use the product and discard product in a manner consistent with the handling of anti-cancer drugs.

Procedures for proper handling and disposal of anticancer drugs should be followed.

Use Aseptic Technique. Aseptic technique must be strictly observed in all handling, since no preservative or bacteriostatic agent is present in DaunoXome or in the materials recommended for dilution.

Withdraw the calculated volume of DaunoXome into a sterile syringe. Instil the DaunoXome preparation into a sterile container with the correct amount of 5% dextrose for infusion. The recommended concentration after dilution is between 0.2 mg and 1 mg daunorubicin/ml of solution. Infuse over a 30-60 minute period. As with all parenteral drug products, inspect the solution visually for particulate matter prior to administration.

Caution: The only fluid which may be mixed with DaunoXome 5% dextrose for infusion; DaunoXome should not be mixed with saline, bacteriostatic agents such as benzyl alcohol, or any other solution.

An in-line filter is not recommended for the intravenous infusion of DaunoXome. However, if such a filter is used, the mean pore diameter of the filter should not be less than 5 micron.

If DaunoXome comes in contact with skin or cornea, wash immediately with copious amounts of cold water. The patient should seek medical attention if signs of inflammation should occur.

DaunoXome should be handled, and any remainder should be disposed of in a manner consistent with the handling of anti-cancer drugs. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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