1. NAME OF THE MEDICINAL PRODUCT

Caelyx liposomal 2 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of Caelyx liposomal contains 2 mg doxorubicin hydrochloride in a pegylated liposomal formulation

Caelyx liposomal, a liposome formulation, is doxorubicin hydrochloride encapsulated in liposomes with surfacebound methoxypolyethylene glycol (MPEG). This process is known as pegylation and protects liposomes from detection by the mononuclear phagocyte system (MPS), which increases blood circulation time.

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Liposome Concentrate for solution for infusion
The suspension is sterile, translucent and red

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Caelyx liposomal is indicated:
- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.
- The treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel and platinium based chemotherapy regimens and who may also be refractory to topotecan. Refractory is defined as a patient having progressive disease while on treatment, or within 6 months of completing treatment.
- 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 and extensive mucocutaneous or visceral disease. **4.2 Posology and method of administration**

Caelyx liposomal should only be administered under the supervision of a qualified oncologist specialized in the administration of cytotoxic agents.

Caelyx liposomal exhibits unique pharmacokinetic properties and must not be used interchangeably with other non-liposomal formulations of doxorubicin hydrochloride.

Posology
Breast cancer/Ovarian cancer:
Caelyx liposomal 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:
Caelyx liposomal 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. 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.

AIDS-related KS:
Caelyx liposomal is administered intravenously at 20 mg/m^2 every two-to-three weeks. Avoid intervals shorter than 10 days as medicinal product accumulation and increased toxicity cannot be ruled out. Treatment of patients for two-to-three months is recommended to achieve a therapeutic response. Continue treatment as needed to maintain a therapeutic response.

For all patients:
If the patient experiences early symptoms or signs of infusion reaction (see sections 4.4 and 4.8), immediately discontinue the infusion, give appropriate premedications (antihistamine and/or short acting corticosteroid) and restart at a slower rate.

Guidelines for Caelyx liposomal 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 Caelyx liposomal 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 trials in the treatment of patients with breast or ovarian cancer only. Dose modification in patients with AIDS-KS is provided following Table 4.

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Table 1. PALMAR–PLANTAR ERYTHRODYSESTHESIA			
	Week after prior Caelyx liposomal 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**	**Withdraw patient**
Grade 4 (diffuse or local process causing infectious complications, or a bedridden state or hospitalisation)	**Wait an additional week**	**Wait an additional week**	**Withdraw patient**

Table 2. STOMATITIS			
Week after prior Caelyx liposomal 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**	**Withdraw patient**
Grade 4 (requires parenteral or enteral support)	**Wait an additional week**	**Wait an additional week**	**Withdraw patient**

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 Caelyx liposomal in combination with bortezomib who experience PPE or stomatitis, the Caelyx liposomal dose should be modified as described in Table 1 and 2 above respectively. Table 4, below provides the schedule followed for other dose modifications in the clinical trial in the treatment of patients with multiple myeloma receiving Caelyx liposomal and bortezomib combination therapy. For more detailed information on bortezomib dosing and dosage adjustments, see the health care professional leaflet for bortezomib.

Table 4. DOSAGE ADJUSTMENTS FOR CAELYX LIPOSOMAL + BORTEZOMIB COMBINATION THERAPY - PATIENTS WITH MULTIPLE MYELOMA		
Patient status	**Caelyx liposomal**	**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	Do not dose until recovered to	Do not dose until recovered to

medicine related toxicity	grade < 2 and reduce dose by 25% for all subsequent doses.	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

For AIDS-KS patients treated with Caelyx liposomal, haematological toxicity may require dose reduction or suspension or delay of therapy. Temporarily suspend Caelyx pegylated liposomal treatment in patients when the ANC count is < 1,000/mm3 and/or the platelet count is < 50,000/mm3. G-CSF (or GM-CSF) may be given as concomitant therapy to support the blood count when the ANC count is < 1,000/mm3 in subsequent cycles.

Hepatic Impairment

Caelyx liposomal 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 Caelyx liposomal dosage in patients with impaired hepatic function should be reduced based on the experience from the breast and ovarian clinical trial programs 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. Caelyx liposomal can be administered to patients with liver metastases with concurrent elevation of bilirubin and liver enzymes up to 4 x the upper limit of the normal range. Prior to Caelyx liposomal administration, evaluate hepatic function using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase, and bilirubin.

Renal Impairment

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

AIDS- related KS patients with splenectomy:
As there is no experience with Caelyx liposomal in patients who have had splenectomy, treatment with Caelyx liposomal is not recommended.

Paediatric population:
The experience in children is limited. Caelyx liposomal is not recommended in patients below 18 years of age.

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

Method of administration

Caelyx liposomal is administered as an intravenous infusion. For further instructions on preparation and special precautions for handling see section 6.6.

Do not administer Caelyx liposomal as a bolus injection or undiluted solution. It is recommended that the Caelyx liposomal infusion line be connected through the side port of an intravenous infusion of 5 % (50 mg/ml) glucose to achieve further dilution and minimise the risk of thrombosis and extravasation. The infusion may be given through a peripheral vein. Do not use with in-line filters. Caelyx liposomal must not be given by the intramuscular or subcutaneous route (see section 6.6).

For doses < 90 mg: dilute Caelyx liposomal in 250 ml 5 % (50 mg/ml) glucose solution for infusion.
For doses ≥ 90 mg: dilute Caelyx liposomal in 500 ml 5 % (50 mg/ml) glucose solution for infusion.

Breast cancer/Ovarian cancer/Multiple Myeloma:

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

In those patients who experience an infusion reaction, the method of infusion should be modified as follows:
5 % of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.

AIDS-related KS:
The dose of Caelyx liposomal is diluted in 250 ml 5 % (50 mg/ml) glucose solution for infusion and administered by intravenous infusion over 30 minutes.

4.3 Contraindications

Hypersensitivity to the active substance , peanut or soya, or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

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

Cardiac toxicity:
It is recommended that all patients receiving Caelyx liposomal 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 Caelyx liposomal 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 Caelyx liposomal therapy and repeated periodically during treatment. The evaluation of left ventricular function is considered to be mandatory before each additional administration of Caelyx liposomal 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 Caelyx liposomal therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

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

Exercise caution in patients with impaired cardiac function who receive Caelyx liposomal .

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 (e.g. < 45 %), 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 (see section 4.8).

Myelosuppression:

Many patients treated with Caelyx liposomal have baseline myelosuppression due to such factors as their pre-existing HIV disease or numerous concomitant or previous medications, or tumours involving bone marrow. In the pivotal trial in patients with ovarian cancer treated at a dose of 50 mg/m^2, myelosuppression was generally mild to moderate, reversible, and was not associated with episodes of neutropaenic infection or sepsis. Moreover, in a controlled clinical trial of Caelyx liposomal vs. topotecan, the incidence of treatment related sepsis was substantially less in the Caelyx liposomal -treated ovarian cancer patients as compared to the topotecan treatment group. A similar low incidence of
myelosuppression was seen in patients with metastatic breast cancer receiving Caelyx liposomal in a first-line clinical trial. In contrast to the experience in patients with breast cancer or ovarian cancer, myelosuppression appears to be the dose-limiting adverse event in patients with AIDS-KS (see section 4.8). Because of the potential for bone marrow suppression, periodic blood counts must be performed frequently during the course of Caelyx liposomal therapy, and at a minimum, prior to each dose of Caelyx liposomal .

Persistent severe myelosuppression, may result in superinfection or haemorrhage.

In controlled clinical studies in patients with AIDS-KS against a bleomycin/vincristine regimen,
opportunistic infections were apparently more frequent during treatment with Caelyx liposomal . 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 Caelyx liposomal or those receiving a cumulative Caelyx liposomal dose greater than 720 mg/m2. Cases of secondary oral cancer were diagnosed both, during treatment with Caelyx liposomal , 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 oedema, chills, back pain, tightness in the chest and throat and/or hypotension may occur within minutes of starting the infusion of Caelyx liposomal . 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 (see section 4.2).

Palmar plantar erythrodysaesthesia syndrome (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 1-2 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, however, these therapies have not been evaluated in phase III trials. 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 (see section 4.2). However, this reaction can be severe and debilitating in some patients and may require discontinuation of treatment (see section 4.8).
Extravasation
Although local necrosis following extravasation has been reported very rarely, Caelyx liposomal 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. Caelyx liposomal must not be given by the intramuscular or subcutaneous route.

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

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

For common adverse events which required dose modification or discontinuation see section 4.8.

4.5 Interaction with other medicinal products and other forms of interaction

No formal medicinal product interaction studies have been performed with Caelyx liposomal , although phase II combination trials with conventional chemotherapy agents have been conducted in patients with gynaecological malignancies. Exercise caution in the concomitant use of medicinal products known to interact with standard doxorubicin hydrochloride. Caelyx liposomal , like other doxorubicin hydrochloride preparations, may potentiate the toxicity of other anti-cancer therapies. During clinical trials 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:
Doxorubicin hydrochloride is suspected to cause serious birth defects when administered during pregnancy. Therefore, Caelyx liposomal 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 Caelyx liposomal and in the six months following discontinuation of Caelyx liposomal therapy (see section 5.3).

Breast-feeding

It is not known whether Caelyx liposomal 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 Caelyx liposomal 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Caelyx liposomal has no or negligible influence on the ability to drive and use machines. However, in clinical studies to date, dizziness and somnolence were associated infrequently (< 5 %) with the administration of Caelyx liposomal . 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 Caelyx liposomal 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 Caelyx liposomal

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, malignant and unspecified (including cysts and polyps)	Not known	Acute myeloid leukaemia[b]
		Myelodysplastic syndrome[b]
		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 disorders[a]	Common	Tachycardia
	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
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 Caelyx liposomal 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). See section 4.4.

Opportunistic infections

Respiratory undesirable effects commonly occurred in clinical studies of Caelyx liposomal and may be related to opportunistic infections (OI's) in the AIDS population. Opportunistic infections are observed in KS patients after administration with Caelyx liposomal, 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 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 Caelyx liposomal greater than 460 mg/m^2 indicate no evidence of anthracycline-induced cardiomyopathy. The recommended dose of Caelyx liposomal 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 Caelyx liposomal 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 %) randomized subjects (10 treated with Caelyx liposomal 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 nomal 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 Caelyx liposomal 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 Caelyx liposomal 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 Caelyx liposomal administration.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form www.sideeffects.health.gov.il

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), ATC code: L01DB01.

Mechanism of action
The active ingredient of Caelyx liposomal 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.

Clinical efficacy and safety
A phase III randomized study of Caelyx liposomal versus doxorubicin in patients with metastatic breast cancer was completed in 509 patients. The protocol-specified objective of demonstrating non-inferiority between Caelyx liposomal and doxorubicin was met, the hazard ratio (HR) for progression-free survival (PFS) was 1.00 (95 % CI for HR=0.82 - 1.22). The treatment HR for PFS when adjusted for prognostic variables was consistent with PFS for the ITT population.

The primary analysis of cardiac toxicity showed the risk of developing a cardiac event as a function of cumulative anthracycline dose was significantly lower with Caelyx liposomal than with doxorubicin (HR=3.16, $p < 0.001$). At cumulative doses greater than 450 mg/m^2 there were no cardiac events with Caelyx liposomal.

A phase III comparative study of Caelyx liposomal versus topotecan in patients with epithelial ovarian cancer following the failure of first-line, platinum based chemotherapy was completed in 474 patients. There was a benefit in overall survival (OS) for Caelyx liposomal-treated patients over topotecan-treated patients as indicated by a hazard ratio (HR) of 1.216 (95 % CI; 1.000, 1.478), p=0.050. The survival rates at 1, 2 and 3 years were 56.3 %, 34.7 % and 20.2 % respectively on Caelyx liposomal, compared to 54.0 %, 23.6 % and 13.2 % on topotecan.

For the sub-group of patients with platinum-sensitive disease the difference was greater: HR of 1.432 (95 % CI; 1.066, 1.923), p=0.017. The survival rates at 1, 2 and 3 years were 74.1 %, 51.2 % and 28.4 % respectively on Caelyx liposomal, compared to 66.2 %, 31.0 % and 17.5 % on topotecan.

The treatments were similar in the sub-group of patients with platinum refractory disease: HR of 1.069 (95 % CI; 0.823, 1.387), p=0.618. The survival rates at 1, 2 and 3 years were 41.5 %, 21.1% and 13.8 % respectively on Caelyx liposomal, compared to 43.2 %, 17.2 % and 9.5 % on topotecan.

A phase III randomized, parallel-group, open-label, multicentre study comparing the safety and efficacy of Caelyx liposomal plus bortezomib combination therapy with bortezomib monotherapy in patients with multiple myeloma who have received at least 1 prior therapy and who did not progress while receiving anthracycline-based therapy, was conducted in 646 patients. There was a significant improvement in the primary endpoint of time to progression (TTP) for patients treated with combination therapy of Caelyx liposomal plus bortezomib compared to patients treated with bortezomib monotherapy as indicated by a risk reduction (RR) of 35 % (95 % CI; 21-47 %), $p < 0.0001$, based on 407 TTP events. The median TTP was 6.9

months for the bortezomib monotherapy patients compared with 8.9 months for the Caelyx liposomal plus bortezomib combination therapy patients. A protocol-defined interim analysis (based on 249 TTP events) triggered early study termination for efficacy. This interim analysis showed a TTP risk reduction of 45 % (95 % CI; 29-57 %), $p < 0.0001$. The median TTP was 6.5 months for the bortezomib monotherapy patients compared with 9.3 months for the Caelyx liposomal plus bortezomib combination therapy patients. These results, though not mature, constituted the protocol defined final analysis. The final analysis for overall survival (OS) performed after a median follow-up of 8.6 years showed no significant difference in OS between the two treatment arms. The median OS was 30.8 months (95% CI; 25.2-36.5 months) for the bortezomib monotherapy patients and 33.0 months (95% CI; 28.9-37.1 months) for the Caelyx liposomal plus bortezomib combination therapy patients.

5.2 Pharmacokinetic properties

Caelyx liposomal 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 Caelyx liposomal 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 Caelyx liposomal 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) Caelyx liposomal displayed linear pharmacokinetics. Over the dose range of 10 mg/m^2 – 60 mg/m^2 Caelyx liposomal 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 Caelyx liposomal indicates that Caelyx liposomal 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 Caelyx liposomal 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.

Caelyx liposomal should not be used interchangeably with other non-liposomal formulations of doxorubicin hydrochloride.

Population pharmacokinetics
The pharmacokinetics of Caelyx liposomal was evaluated in 120 patients from 10 different clinical trials using the population pharmacokinetic approach. The pharmacokinetics of Caelyx liposomal over the dose range of 10 mg/m^2 to 60 mg/m^2 was best described by a two compartment non-linear model with zero order input and Michaelis-Menten elimination. The mean intrinsic clearance of Caelyx liposomal was 0.030 l/h/m^2 (range 0.008 to 0.152 l/h/m^2) and the mean central volume of distribution was 1.93 l/m^2 (range 0.96 – 3.85 l/m^2) approximating the plasma volume. The apparent half-life ranged from 24 – 231 hours, with a mean of 73.9 hours.

Breast cancer patients
The pharmacokinetics of Caelyx liposomal determined in 18 patients with breast carcinoma were similar to the pharmacokinetics determined in the larger population of 120 patients with various cancers. The mean intrinsic clearance was 0.016 l/h/m^2 (range 0.008 - 0.027 l/h/m^2), the mean central volume of distribution was 1.46 l/m^2 (range 1.10 - 1.64 l/m^2). The mean apparent half-life was 71.5 hours (range 45.2 - 98.5 hours).

Ovarian cancer patients
The pharmacokinetics of Caelyx liposomal determined in 11 patients with ovarian carcinoma were similar to the pharmacokinetics determined in the larger population of 120 patients with various cancers. The mean intrinsic clearance was 0.021 l/h/m^2 (range 0.009 – 0.041 l/h/m^2), the mean central volume of distribution was 1.95 l/m^2 (range 1.67 – 2.40 l/m^2). The mean apparent half-life was 75.0 hours (range 36.1 – 125 hours).

AIDS-related KS patients
The plasma pharmacokinetics of Caelyx liposomal were evaluated in 23 patients with KS who received single doses of 20 mg/m^2 administered by a 30-minute infusion. The pharmacokinetic parameters of Caelyx liposomal (primarily representing pegylated liposomal doxorubicin hydrochloride and low levels of unencapsulated doxorubicin hydrochloride) observed after the 20 mg/m^2 doses are presented in Table 6.

Table 6. Pharmacokinetic Parameters in Caelyx liposomal -Treated AIDS-KS Patients

	Mean ± Standard Error
Parameter	20 mg/m^2 (n=23)
Maximum Plasma Concentration* (µg/ml)	8.34 ± 0.49
Plasma Clearance (l/h/m^2)	0.041 ± 0.004
Volume of Distribution (l/m^2)	2.72 ± 0.120
AUC (µg/ml·h)	590.00 ± 58.7
λ_1 half-life (hours)	5.2 ± 1.4
λ_2 half-life (hours)	55.0 ± 4.8

*Measured at the end of a 30-minute infusion

5.3 Preclinical safety data

In repeat dose studies conducted in animals, the toxicity profile of Caelyx liposomal appears very similar to that reported in humans who receive long-term infusions of standard doxorubicin hydrochloride. With Caelyx liposomal, the encapsulation of doxorubicin hydrochloride in pegylated liposomes results in these effects having a differing strength, as follows.

Cardiotoxicity:
Studies in rabbits have shown that the cardiotoxicity of Caelyx liposomal is reduced compared with conventional doxorubicin hydrochloride preparations.

Dermal toxicity:
In studies performed after the repeated administration of Caelyx liposomal to rats and dogs, serious dermal inflammations and ulcer formations were observed at clinically relevant dosages. In the study in dogs, the occurrence and severity of these lesions was reduced by lowering the dose or prolonging the intervals between doses. Similar dermal lesions, which are described as palmar-plantar erythrodysesthesia were also observed in patients after long-term intravenous infusion (see section 4.8).

Anaphylactoid response:
During repeat dose toxicology studies in dogs, an acute response characterised by hypotension, pale mucous membranes, salivation, emesis and periods of hyperactivity followed by hypoactivity and lethargy was observed following administration of pegylated liposomes (placebo). A similar, but less severe response was also noted in dogs treated with Caelyx liposomal and standard doxorubicin.

The hypotensive response was reduced in magnitude by pretreatment with antihistamines. However, the response was not life-threatening and the dogs recovered quickly upon discontinuation of treatment.

Local toxicity:
Subcutaneous tolerance studies indicate that Caelyx liposomal, as against standard doxorubicin hydrochloride, causes slighter local irritation or damage to the tissue after a possible extravasation.

Mutagenicity and carcinogenicity:
Although no studies have been conducted with Caelyx liposomal, doxorubicin hydrochloride, the pharmacologically active ingredient of Caelyx liposomal, is mutagenic and carcinogenic. Pegylated placebo liposomes are neither mutagenic nor genotoxic.

Reproductive toxicity:
Caelyx liposomal resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 mg/kg. Decreased testicular weights and hypospermia were present in rats after repeat doses ≥ 0.25 mg/kg/day and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis were observed in dogs after repeat doses of 1 mg/kg/day (see section 4.6).

Nephrotoxicity:
A study has shown that Caelyx liposomal at a single intravenous dose of over twice the clinical dose produces renal toxicity in monkeys. Renal toxicity has been observed with even lower single doses of doxorubicin HCl in rats and rabbits. Since an evaluation of the post-marketing safety database for Caelyx liposomal in patients has not suggested a significant nephrotoxicity liability of Caelyx liposomal, these findings in monkeys may not have relevance to patient risk assessment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

α-(2-[1,2-distearoyl-*sn*-glycero(3)phosphooxy]ethylcarbamoyl)-ω-methoxypoly(oxyethylen)-40 sodium salt (MPEG-DSPE)
fully hydrogenated soy phosphatidylcholine (HSPC)
cholesterol
ammonium sulphate
sucrose
histidine
water for injections
hydrochloric acid (for pH-adjustment)
sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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.

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).
Caelyx liposomal is supplied as a single pack.

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 Caelyx liposomal solution. The use of gloves is required. If Caelyx liposomal comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. Caelyx liposomal 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 Caelyx liposomal to be administered (based upon the recommended dose and the patient's body surface area). Take the appropriate volume of Caelyx liposomal up into a sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Caelyx liposomal. The appropriate dose of Caelyx liposomal must be diluted in 5 % (50 mg/ml) glucose solution for infusion prior to administration. For doses < 90 mg, dilute Caelyx liposomal in 250 ml, and for doses ≥ 90 mg, dilute Caelyx liposomal in 500 ml. This can be infused over 60 or 90 minutes as detailed in 4.2.

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 Caelyx liposomal.

It is recommended that the Caelyx liposomal 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.

7. MARKETING AUTHORISATION HOLDER

J-C Health Care Ltd.
Kibbitz Shefayim
6099000
Israel

8. MANUFACTURER

Janssen Pharmaceutica
Beerse
Belgium

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