ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Caelyx 2 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Caelyx, a liposome formulation, is doxorubicin hydrochloride encapsulated in liposomes with surface-bound 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

The suspension is sterile, translucent and red.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Caelyx is indicated:
- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.
- 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.

Caelyx 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

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

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

Posology
Breast cancer/Ovarian cancer
Caelyx 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 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 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 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 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 addressed in section 4.8.

Table 1. Palmar–Plantar erythrodysesthesia

	Week after prior Caelyx 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 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 in combination with bortezomib who experience PPE or stomatitis, the Caelyx 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 and bortezomib

combination therapy. For more detailed information on bortezomib dosing and dosage adjustments, see the SPC for bortezomib.

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

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

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

Hepatic Impairment
Caelyx 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 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 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 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 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 in patients who have had splenectomy, treatment with Caelyx is not recommended.

Paediatric population
The experience in children is limited. Caelyx 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.

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

Do not administer Caelyx as a bolus injection or undiluted solution. It is recommended that the Caelyx 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 must not be given by the intramuscular or subcutaneous route (see section 6.6).

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

Breast cancer/Ovarian cancer/Multiple myeloma
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 Caelyx 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 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 or to any of the excipients listed in section 6.1.

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

Cardiac toxicity
It is recommended that all patients receiving Caelyx 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 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 therapy and repeated periodically during treatment. The evaluation of left ventricular function is considered to be mandatory before each additional administration of Caelyx 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 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 only when the benefit outweighs the risk to the patient.

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

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 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 vs. topotecan, the incidence of treatment related sepsis was substantially less in the Caelyx-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 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 therapy, and at a minimum, prior to each dose of Caelyx.

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. 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 or those receiving a cumulative Caelyx dose greater than 720 mg/m^2. Cases of secondary oral cancer were diagnosed both, during treatment with Caelyx, 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. Very rarely, convulsions also have been observed in relation to infusion reactions (see section 4.8). 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).

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

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, 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, 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 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 and in the six months following discontinuation of Caelyx therapy (see section 5.3).

Breast-feeding
It is not known whether Caelyx 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 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 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. Patients who suffer from these effects must avoid driving and operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most common undesirable effect reported in breast/ovarian clinical trials (50 mg/m^2 every 4 weeks) was palmar-plantar erythrodysesthesia (PPE). The overall incidence of PPE reported was 44.0%-46.1%. These effects were mostly mild, with severe (grade 3) cases reported in 17%-19.5%. The reported incidence of life-threatening (grade 4) cases was < 1%. PPE infrequently resulted in permanent treatment discontinuation (3.7%-7.0%). PPE is characterised by painful, macular reddening skin eruptions. In patients experiencing this event, it is generally seen after two or three cycles of treatment. Improvement usually occurs in one - two weeks, and in some cases, may take up to 4 weeks or longer for complete resolution. Pyridoxine at a dose of 50-150 mg per day and corticosteroids have been used for the prophylaxis and treatment of PPE, 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. Stomatitis/mucositis and nausea were also commonly reported in breast/ovarian cancer patient populations, whereas the AIDS-KS Program (20 mg/m^2 every 2 weeks), myelosuppression (mostly leukopaenia) was the most common side effect (see AIDS-KS). PPE was reported in 16% of multiple myeloma patients treated with Caelyx plus bortezomib combination therapy. Grade 3 PPE was reported in 5% of patients. No grade 4 PPE was reported. The most frequently reported (medicine-related treatment-emergent) adverse events in combination therapy (Caelyx + bortezomib) were nausea (40%), diarrhoea (35%), neutropaenia (33%), thrombocytopaenia (29%), vomiting (28%), fatigue (27%), and constipation (22%).

Breast cancer program

509 patients with advanced breast cancer who had not received prior chemotherapy for metastatic disease were treated with Caelyx (n=254) at a dose of 50 mg/m^2 every 4 weeks, or doxorubicin (n=255) at a dose of 60 mg/m^2 every 3 weeks, in a phase III clinical trial (I97-328). The following common adverse events were reported more often with doxorubicin than with Caelyx: nausea (53% vs. 37%; grade 3/4 5% vs. 3%), vomiting (31% vs. 19%; grade 3/4 4% vs. less than 1%), any alopecia (66% vs. 20%), pronounced alopecia (54% vs.7%), and neutropaenia (10% vs. 4%; grade 3/4 8% vs. 2%).

Mucositis (23% vs. 13%; grade 3/4 4% vs. 2%), and stomatitis (22% vs. 15%; grade 3/4 5% vs. 2%) were reported more commonly with Caelyx than with doxorubicin. The average duration of the most common severe (grade 3/4) events for both groups was 30 days or less. See Table 5 for complete listing of undesirable effects reported in Caelyx-treated patients.

The incidence of life threatening (grade 4) haematologic effects was < 1.0% and sepsis was reported in 1% of patients. Growth factor support or transfusion support was necessary in 5.1% and 5.5% of patients, respectively (see section 4.2).

Clinically significant laboratory abnormalities (grades 3 and 4) in this group was low with elevated total bilirubin, AST and ALT reported in 2.4%, 1.6% and < 1% of patients respectively. No clinically significant increases in serum creatinine were reported.

Table 5. Treatment related undesirable effects reported in breast cancer clinical trials (50 mg/m^2 every 4 weeks) (Caelyx-treated patients) by severity, MedDRA system organ class and preferred term

Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, < 1/100)

CIOMS III

AE by body system	Breast cancer All severities n=254 (≥ 5%)	Breast cancer Grades 3/4 n=254 (≥ 5%)	Breast cancer n=404 (1-5%) not previously reported in clinical trials
Infections and infestations			
Common	Pharyngitis		Folliculitis, fungal infection, cold sores (non-herpetic), upper respiratory tract infection
Uncommon		Pharyngitis	
Blood and lymphatic system disorders			
Common	Leukopaenia, anaemia, neutropaenia, thrombocytopaenia	Leukopaenia, anaemia	Thrombocythemia
Uncommon		Neutropaenia	
Metabolism and nutrition disorders			
Very common	Anorexia		
Common		Anorexia	
Nervous system disorders			
Common	Paresthesia	Paresthesia	Peripheral neuropathy
Uncommon	Somnolence		
Eye disorders			
Common			Lacrimation, blurred vision
Cardiac disorders			
Common			Ventricular arrhythmia
Respiratory, thoracic and mediastinal disorders			
Common			Epistaxis
Gastrointestinal disorders			
Very common	Nausea, stomatitis, vomiting		
Common	Abdominal pain, constipation, diarrhoea, dyspepsia, mouth ulceration	Abdominal pain, diarrhoea, nausea, stomatitis	Oral pain
Uncommon		Mouth ulceration, constipation, vomiting	
Skin and subcutaneous tissue disorders			
Very common	PPE*, alopecia, rash	PPE*	

Common	Dry skin, skin discolouration, pigmentation abnormal, erythema	Rash	Bullous eruption, dermatitis, erythematous rash, nail disorder, scaly skin
Uncommon		Pigmentation abnormal, erythema	
Musculoskeletal and connective tissue disorders			
Common			Leg cramps, bone pain, musculoskeletal pain
Reproductive system and breast disorders			
Common			Breast pain
General disorders and administration site conditions			
Very common	Asthenia, fatigue, mucositis NOS		
Common	Weakness, fever, pain	Asthenia, mucositis NOS	Oedema, leg oedema.
Uncommon		Fatigue, weakness, pain	

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

Ovarian cancer program

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

Table 6. Treatment related undesirable effects reported in ovarian cancer clinical trials (50 mg/m^2 every 4 weeks) (Caelyx-treated patients) by severity, MedDRA system organ class and preferred term

Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, < 1/100)

CIOMS III

AE by body system	Ovarian cancer All severities n=512 (≥ 5%)	Ovarian cancer Grades 3/4 n=512 (≥ 5%)	Ovarian cancer n=512 (1-5%)
Infections and infestations			
Common	Pharyngitis		Infection, oral moniliasis, herpes zoster, urinary tract infection
Uncommon		Pharyngitis	
Blood and lymphatic system disorders			
Very common	Leukopaenia, anaemia, neutropaenia, thrombocytopaenia	Neutropaenia	
Common		Leukopaenia, anaemia, thrombocytopaenia	Hypochromic anaemia
Immune system disorders			
Common			Allergic reaction

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

General disorders and administration site conditions			
Very common	Asthenia, mucous membrane disorder		
Common	Fever, pain	Asthenia, mucous membrane disorder, pain	Chills, chest pain, malaise, peripheral oedema
Uncommon		Fever	
Investigations			
Common			Weight loss

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

Myelosuppression was mostly mild or moderate and manageable. Sepsis related to leukopaenia was observed infrequently (< 1%). Growth factor support was required infrequently (< 5%) and transfusion support was required in approximately 15% of patients (see section 4.2).

In a subset of 410 patients with ovarian cancer, clinically significant laboratory abnormalities occurring in clinical trials with Caelyx included increases in total bilirubin (usually in patients with liver metastases) (5%) and serum creatinine levels (5%). Increases in AST were less frequently (< 1%) reported.

Solid tumour patients: in a larger cohort of 929 patients with solid tumours (including breast cancer and ovarian cancer) predominantly treated at a dose of 50 mg/m^2 every 4 weeks, the safety profile and incidence of adverse effects are comparable to those of the patients treated in the pivotal breast cancer and ovarian cancer trials.

Multiple myeloma program

Of 646 patients with multiple myeloma who have received at least 1 prior therapy, 318 patients were treated with combination therapy of Caelyx 30 mg/m^2 as a one hour intravenous infusion administered on day 4 following bortezomib which is administered at 1.3 mg/m² on days 1, 4, 8, and 11, every three weeks or with bortezomib monotherapy in a phase III clinical trial. See Table 7 for adverse effects reported in ≥ 5% patients treated with combination therapy of Caelyx plus bortezomib.

Neutropaenia, thrombocytopaenia, and anaemia were the most frequently reported hematologic events reported with both combination therapy of Caelyx plus bortezomib and bortezomib monotherapy. The incidence of grade 3 and 4 neutropaenia was higher in the combination therapy group than in the monotherapy group (28% vs. 14%). The incidence of grade 3 and 4 thrombocytopaenia was higher in the combination therapy group than in the monotherapy group (22% vs. 14%). The incidence of anaemia was similar in both treatment groups (7% vs. 5%).

Stomatitis was reported more frequently in the combination therapy group (16%) than in the monotherapy group (3%), and most cases were grade 2 or less in severity. Grade 3 stomatitis was reported in 2% of patients in the combination therapy group. No grade 4 stomatitis was reported.

Nausea and vomiting were reported more frequently in the combination therapy group (40% and 28%) than in the monotherapy group (32% and 15%) and were mostly grade 1 and 2 in severity.

Treatment discontinuation of one or both agents due to adverse events was seen in 38% of patients. Common adverse events which led to treatment discontinuation of bortezomib and Caelyx included PPE, neuralgia, peripheral neuropathy, peripheral sensory neuropathy, thrombocytopaenia, decreased ejection fraction, and fatigue.

Table 7. Treatment related undesirable effects reported in multiple myeloma clinical trial (Caelyx 30 mg/m^2 in combination with bortezomib every 3 weeks) by severity, MedDRA system organ class and preferred term
Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, < 1/100)

CIOMS III

AE by body system	All Severities n=318 (≥ 5%)	Grades 3/4** n=318 (≥ 5%)	All Severities n=318 (1-5%)
Infections and infestations			
Common	Herpes simplex, herpes zoster	Herpes zoster	Pneumonia, nasopharyngitis, upper respiratory tract infection, oral candidiasis
Blood and lymphatic system disorders			
Very common	Anaemia, neutropaenia, thrombocytopaenia	Neutropaenia, thrombocytopaenia	
Common	Leukopaenia	Anaemia, leukopaenia	Febrile neutropaenia, lymphopaenia
Metabolism and nutrition disorders			
Very common	Anorexia		
Common	Decreased appetite	Anorexia	Dehydration, hypokalaemia, hyperkalaemia, hypomagnesaemia, hyponatraemia, hypocalcaemia
Uncommon		Decreased appetite	
Psychiatric disorders			
Common	Insomnia		Anxiety
Nervous system disorders			
Very common	Peripheral sensory neuropathy, neuralgia, headache		
Common	Neuropathy peripheral, neuropathy, paraesthesia, polyneuropathy, dizziness, dysgeusia	Neuralgia, peripheral neuropathy, neuropathy	Lethargy, hypoaesthesia, syncope, dysaesthesia
Uncommon		Headache, peripheral sensory neuropathy, paraesthesia, dizziness	
Eye disorders			
Common			Conjunctivitis
Vascular disorders			
Common			Hypotension, orthostatic hypotension, flushing, hypertension, phlebitis

Respiratory, thoracic and mediastinal disorders			
Common	Dyspnoea		Cough, epistaxis exertional dyspnoea
Uncommon		Dyspnoea	
Gastrointestinal disorders			
Very common	Nausea, diarrhoea, vomiting, constipation, stomatitis		
Common	Abdominal pain, dyspepsia	Nausea, diarrhoea, vomiting, stomatitis	Upper abdominal pain, mouth ulceration, dry mouth, dysphagia, aphthous stomatitis
Uncommon		Constipation, abdominal pain, dyspepsia	
Skin and subcutaneous tissue disorders			
Very common	PPE*, rash		
Common	Dry skin	PPE*	Pruritus, papular rash, allergic dermatitis, erythema, skin hyperpigmentation, petechiae, alopecia, medicine eruption
Uncommon		Rash	
Musculoskeletal and connective tissue disorders			
Common	Pain in extremity		Arthralgia, myalgia, muscle spasms, muscular weakness, musculoskeletal pain, musculoskeletal chest pain
Reproductive system and breast disorders			
Common			Scrotal erythema
General disorders and administration site conditions			
Very common	Asthenia, fatigue, pyrexia		
Common		Asthenia, fatigue	Peripheral oedema, chills, influenza-like illness, malaise, hyperthermia
Uncommon		Pyrexia	
Investigations			
Common	Weight decreased		Aspartate aminotransferase increased, ejection fraction decreased, blood creatinine increased, alanine aminotransferase increased

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

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

AIDS-related KS program

Clinical studies on AIDS-KS patients treated at 20 mg/m^2 with Caelyx show that myelosuppression was the most frequent undesirable effect considered related to Caelyx occurring very commonly (in approximately one-half of the patients).

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

Respiratory undesirable effects commonly occurred in clinical studies of Caelyx and may be related to opportunistic infections in the AIDS population. Opportunistic infections (OI's) are observed in KS patients after administration with Caelyx, 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 carinii* pneumonia, and mycobacterium avium complex.

Table 8. Undesirable effects observed in patients with AIDS-related KS according to CIOMS III frequency categories
Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, < 1/100)

Infections and infestations	
common	oral moniliasis
Blood and lymphatic system disorders	
very common	neutropaenia, anaemia, leukopaenia
common	thrombocytopaenia
Metabolism and nutrition disorders	
common	anorexia
Psychiatric disorders	
uncommon	confusion
Nervous system disorders	
common	dizziness
uncommon	paresthesia
Eye disorders	
common	retinitis
Vascular disorders	
common	vasodilatation
Respiratory, thoracic and mediastinal disorders	
common	dyspnoea
Gastrointestinal disorders	
very common	nausea
common	diarrhoea, stomatitis, vomiting, mouth ulceration, abdominal pain, glossitis, constipation, nausea and vomiting

Skin and subcutaneous tissue disorders	
common	alopecia, rash
uncommon	palmar-plantar erythrodysesthesia (PPE)
General disorders and administration site conditions	
common	asthenia, fever, infusion-associated acute reactions
Investigations	
common	weight loss

Other less frequently (< 5%) observed undesirable effects included hypersensitivity reactions including anaphylactic reactions. Following marketing, bullous eruption has been reported rarely in this population.

Clinically significant laboratory abnormalities frequently (≥ 5%) occurred including increases in alkaline phosphatase; AST and bilirubin which were believed to be related to the underlying disease and not Caelyx. Reduction in haemoglobin and platelets were less frequently (< 5%) reported. Sepsis related to leukopaenia was rarely (< 1%) observed. Some of these abnormalities may have been related to the underlying HIV infection and not Caelyx.

All patients
100 out of 929 patients (10.8%) with solid tumours were described as having an infusion-associated reaction during treatment with Caelyx as defined by the following Costart terms: allergic reaction, anaphylactoid reaction, asthma, face oedema, hypotension, vasodilatation, urticaria, back pain, chest pain, chills, fever, hypertension, tachycardia, dyspepsia, nausea, dizziness, dyspnoea, pharyngitis, rash, pruritus, sweating, injection site reaction and medicinal product interaction. Permanent treatment discontinuation was infrequently reported at 2%. A similar incidence of infusion reactions (12.4%) and treatment discontinuation (1.5%) was observed in the breast cancer program**.** In patients with multiple myeloma receiving Caelyx plus bortezomib, infusion-associated reactions have been reported at a rate of 3%. In patients with AIDS-KS, infusion-associated reactions, were characterised by flushing, shortness of breath, facial oedema, headache, chills, back pain, tightness in the chest and throat and/or hypotension and can be expected at the rate of 5% to 10%. Very rarely, convulsions have been observed in relation to infusion reactions. In all patients, infusion-associated reactions occurred primarily during the first infusion. Temporarily stopping the infusion usually resolves these symptoms without further therapy. In nearly all patients, Caelyx treatment can be resumed after all symptoms have resolved without recurrence. Infusion reactions rarely recur after the first treatment cycle with Caelyx (see section 4.2).

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

Stomatitis has been reported in patients receiving continuous infusions of conventional doxorubicin hydrochloride and was frequently reported in patients receiving Caelyx. It did not interfere with patients completing therapy and no dosage adjustments are generally required, unless stomatitis is affecting a patient's ability to eat. In this case, the dose interval may be extended by 1-2 weeks or the dose reduced (see section 4.2).

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 greater than 460 mg/m^2 indicate no evidence of anthracycline-induced cardiomyopathy. The recommended dose of Caelyx 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 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 Caelyx 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 Caelyx 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 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.

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

Although local necrosis following extravasation has been reported very rarely, Caelyx 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 must not be given by the intramuscular or subcutaneous route.

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

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

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1,000 and < 1/100
Rare	≥ 1/10,000, < 1/1,000
Very rare	< 1/10,000 including isolated reports

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

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
very rare	secondary oral neoplasms[1]
Vascular disorders	
uncommon	venous thromboembolism, including thrombophlebitis, venous thrombosis and pulmonary embolism

Skin and subcutaneous tissue disorders	
very rare	erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis

[1] Cases of secondary oral cancer have been reported in patients with long-term (more than one year) exposure to Caelyx or those receiving a cumulative Caelyx dose greater than 720 mg/m^2 (see section 4.4).

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 the national reporting system listed in Appendix V.

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.

Mechansim of action
The active ingredient of Caelyx 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 randomised study of Caelyx versus doxorubicin in patients with metastatic breast cancer was completed in 509 patients. The protocol-specified objective of demonstrating non-inferiority between Caelyx 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 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.

A phase III comparative study of Caelyx 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-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, 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, 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, compared to 43.2%, 17.2% and 9.5% on topotecan.

A phase III randomised, parallel-group, open-label, multicentre study comparing the safety and efficacy of Caelyx 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 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 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 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 plus bortezomib combination therapy patients.

5.2 Pharmacokinetic properties

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

<u>Population pharmacokinetics</u>
The pharmacokinetics of Caelyx was evaluated in 120 patients from 10 different clinical trials using the population pharmacokinetic approach. The pharmacokinetics of Caelyx 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 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 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 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 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 (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 10.

Table 10. Pharmacokinetic parameters in Caelyx-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 appears very similar to that reported in humans who receive long-term infusions of standard doxorubicin hydrochloride. With Caelyx, 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 is reduced compared with conventional doxorubicin hydrochloride preparations.

Dermal toxicity
In studies performed after the repeated administration of Caelyx 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 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, 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, doxorubicin hydrochloride, the pharmacologically active ingredient of Caelyx, is mutagenic and carcinogenic. Pegylated placebo liposomes are neither mutagenic nor genotoxic.

Reproductive toxicity
Caelyx 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 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 in patients has not suggested a significant nephrotoxicity liability of Caelyx, 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
sodium hydroxide

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

20 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.

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 is supplied as a single pack or packs of ten vials.

Not all pack sizes may be marketed.

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

It is recommended that the Caelyx 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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/011/001
EU/1/96/011/002
EU/1/96/011/003
EU/1/96/011/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 June 1996
Date of lastest renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse, Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CAELYX CARTON 20 mg/10 ml – 1 vial
CAELYX CARTON 20 mg/10 ml – 10 vials

1. NAME OF THE MEDICINAL PRODUCT

Caelyx 2 mg/ml concentrate for solution for infusion
Pegylated liposomal doxorubicin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of Caelyx contains 2 mg pegylated liposomal doxorubicin hydrochloride.

3. LIST OF EXCIPIENTS

Excipients: α-(2-[1,2-distearoyl-*sn*-glycero(3)phosphooxy]ethylcarbamoyl)-ϖ-methoxypoly(oxyethylen)-40 sodium salt, fully hydrogenated soy phosphatidylcholine, cholesterol, ammonium sulphate, sucrose, histidine, water for injections, hydrochloric acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial
10 vials
20 mg/10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use, following dilution in 5% (50 mg/ml) glucose solution for infusion.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

DO NOT USE INTERCHANGEABLY WITH OTHER FORMULATIONS OF DOXORUBICIN HYDROCHLORIDE.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Partially used vials should be discarded.

Cytotoxic

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/011/001 (1 vial)
EU/1/96/011/002 (10 vials)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Caelyx 20 mg/10 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CAELYX CARTON 50 mg/25 ml – 1 vial
CAELYX CARTON 50 mg/25 ml – 10 vials

1. NAME OF THE MEDICINAL PRODUCT

Caelyx 2 mg/ml concentrate for solution for infusion
Pegylated liposomal doxorubicin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of Caelyx contains 2 mg pegylated liposomal doxorubicin hydrochloride.

3. LIST OF EXCIPIENTS

Excipients: α-(2-[1,2-distearoyl-*sn*-glycero(3)phosphooxy]ethylcarbamoyl)-ϖ-methoxypoly(oxyethylen)-40 sodium salt, fully hydrogenated soy phosphatidylcholine, cholesterol, ammonium sulphate, sucrose, histidine, water for injections, hydrochloric acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial
10 vials
50 mg/25 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use, following dilution in 5% (50 mg/ml) glucose solution for infusion.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

DO NOT USE INTERCHANGEABLY WITH OTHER FORMULATIONS OF DOXORUBICIN HYDROCHLORIDE.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Partially used vials should be discarded.

Cytotoxic

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/011/003 (1 vial)
EU/1/96/011/004 (10 vials)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Caelyx 50 mg/25 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CAELYX LABEL 20 mg/10 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Caelyx 2 mg/ml concentrate for solution for infusion
Pegylated liposomal doxorubicin hydrochloride

Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mg/10 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CAELYX LABEL 50 mg/25 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Caelyx 2 mg/ml concentrate for solution for infusion
Pegylated liposomal doxorubicin hydrochloride

Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg/25 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: information for the user

Caelyx 2 mg/ml concentrate for solution for infusion
Pegylated liposomal doxorubicin hydrochloride

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Caelyx is and what it is used for

Caelyx is an antitumour agent.

Caelyx is used to treat cancer of the breast in patients at risk for heart problems. Caelyx is also used to treat cancer of the ovary. It is used to kill cancer cells, shrink the size of the tumour, delay the growth of the tumour, and extend your survival.

Caelyx is also used in combination with another medicine, bortezomib, to treat multiple myeloma, a cancer of the blood in patients who have received at least 1 prior therapy.

Caelyx is also used to produce an improvement in your Kaposi's sarcoma including flattening, lightening and even shrinkage of the cancer. Other symptoms of Kaposi's sarcoma, such as swelling around the tumour, may also improve or disappear.

Caelyx contains a medicine which is able to interact with cells in such a way as to selectively kill cancer cells. The doxorubicin hydrochloride in Caelyx is enclosed in tiny spheres called pegylated liposomes which help to deliver the medicinal product from the blood stream to the cancerous tissue rather than healthy normal tissue.

2. What you need to know before you use Caelyx

Do not use Caelyx
- if you are allergic to doxorubicin hydrochloride or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
You should tell your doctor about any of the following:
- if you are receiving any treatment for heart disease or liver disease;
- if you are diabetic, because Caelyx contains sugar which may require an adjustment to the treatment of your diabetes;
- if you have Kaposi's sarcoma and have had your spleen removed;
- if you notice sores, discolouration or any discomfort in your mouth.

Children and adolescents
Caelyx should not be used in children and adolescents, because it is not known how the medicine will affect them.

Other medicines and Caelyx
Tell your doctor or pharmacist
- if you are taking or have recently taken any other medicines, including medicines obtained without a prescription;
- about any other cancer treatments you are on or have been taking, as particular care needs to be taken with treatments which reduce the number of white blood cells, as this may cause further reduction in the number of white blood cells. If you are unsure about what treatments you have received or any illnesses you have had, discuss these with your doctor.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Because the active ingredient doxorubicin hydrochloride in Caelyx may cause birth defects, it is important to tell your doctor if you think you are pregnant. Avoid becoming pregnant while you or your partner are taking Caelyx and in the six months following discontinuation of Caelyx treatment.

Because doxorubicin hydrochloride may be harmful to nursing infants, women must discontinue breast-feeding before starting treatment with Caelyx. Health experts recommend that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Driving and using machines
Do not drive or use any tools or machines if you feel tired or sleepy from treatment with Caelyx.

3. How to use Caelyx

Caelyx is a unique formulation. It must not be used interchangeably with other formulations of doxorubicin hydrochloride.

How much Caelyx is given
If you are being treated for breast cancer or ovarian cancer, Caelyx will be administered at a dose of 50 mg per square metre of your body surface area (based on your height and weight). The dose is repeated every 4 weeks for as long as the disease does not progress and you are able to tolerate the treatment.

If you are being treated for multiple myeloma, and have already received at least 1 prior therapy, Caelyx will be administered at a dose of 30 mg per square metre of your body surface area (based on your height and weight) as a 1 hour intravenous infusion on day 4 of the bortezomib 3 week regimen immediately after the bortezomib infusion. The dose is repeated as long as you respond satisfactorily and tolerate treatment.

If you are being treated for Kaposi'sarcoma, Caelyx will be administered at a dose of 20 mg per square metre of your body surface area (based on your height and weight). The dose is repeated every 2 to 3 weeks for 2-3 months, then as often as necessary to maintain an improvement in your condition.

How Caelyx is given
Caelyx will be given to you by your doctor in a drip (infusion) into a vein. Depending on the dose and indication, this may take from 30 minutes to more than one hour (i.e., 90 minutes).

If you use more Caelyx than you should
Acute overdosing worsens side effects like sores in the mouth or decreases the number of white blood cells and platelets in the blood. Treatment will include administration of antibiotics, platelet cell

transfusions, use of factors which stimulate production of white blood cells and symptomatic treatment of mouth sores.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

During the infusion of Caelyx, the following reactions may occur: flushing of the face, shortness of breath, headache, chills, back pain, tightness in the chest and/or throat, sore throat, low or increase in blood pressure, rapid heart beat, puffing of the face, fever, dizziness, nausea, indigestion, itching, rash and sweating. In very rare cases, seizures (convulsions) have occurred. Stinging or swelling of the skin at the site of injection may also occur. If the drip stings or hurts while you are receiving a dose of Caelyx, tell your doctor immediately.

Contact your doctor immediately if:
- you get reddening painful skin on your hands and feet;
- you get painful reddening of the skin and/or blisters on the body or in the mouth;
- you get heart problems;
- you get mouth sores;
- you develop a fever or any other sign of an infection;
- you get sudden shortness of breath or sharp chest pain that may worsen with deep breathing or coughing;
- you get swelling, warmth, or tenderness in the soft tissues of your leg, sometimes with pain which gets worse when you stand or walk.

Other side effects
Between infusions, the following may occur:

Very common side effects (may affect more than 1 in 10 people)
- redness, swelling and sores on the palms of your hands and feet. These effects have been seen frequently, and are sometimes severe. In severe cases, these effects may interfere with certain daily activities, and may last for 4 weeks or longer before resolving completely. The doctor may wish to delay the start and/or reduce the dose of the next treatment (see Strategies to prevent and treat hand-foot syndrome, below);
- pain or sores in mouth or throat, nausea, vomiting, diarrhoea, constipation, loss of appetite, weight loss;
- decrease in the number of white blood cells, which can increase the chances of infections. Anaemia (reduction in red blood cells) may cause tiredness, and decreased platelets in the blood may increase the risk of bleeding. In rare cases, having low white blood cells may lead to severe infection. It is because of the potential changes in your blood cells that you will have regular blood tests. From a clinical study in patients with AIDS-KS comparing Caelyx against another treatment (bleomycin/vincristine), there may be a higher chance of some infections with Caelyx. However, in contrast to the experience with patients with AIDS-KS, when Caelyx was compared to a standard treatment for advanced ovarian cancer (topotecan), the risk of infections was substantially lower in the Caelyx-treated patients. The risk of low blood counts and infections was similarly low in breast cancer studies. Some of these effects may be related to your disease and not to Caelyx;
- general feeling of tiredness, weakness, feeling of pins and needles or pain in hands and feet;
- hair loss.

Common side effects (may affect up to 1 in 10 people)
- stomach pain;
- oral thrush (a fungal infection in the mouth), sores in nose, bleeding from your nose, cold sores, and tongue inflammation;

- laboratory values related to the function of the liver may either increase or decrease while on Caelyx;
- sleepiness, dizziness, fainting, bone pain, breast pain, abnormal muscle tension, muscle pain, leg cramps or swelling, general swelling, inflammation of the retina (the light-detecting membrane of the eye), increased tear production, blurred vision, feeling of pins and needles or pain in hands and feet;
- inflammation of hair follicles, scaly skin, inflammation or rash, abnormal skin pigmentation (colouring), and nail disorder;
- heart problems, e.g., irregular heart beat, enlarged blood vessels;
- fever, increased temperature or any other sign of infection which may be related to your disease;
- respiratory problems, i.e., difficulty in breathing or coughing which may be linked to infections you have caught as a result of your disease;
- not enough water in the body (dehydration), severe weight loss and muscle wasting, low levels of calcium, magnesium, potassium or sodium in the blood, high levels of potassium in the blood;
- inflamed foodpipe, inflamed stomach lining, difficulty swallowing, dry mouth, passing wind, inflamed gums (gingivitis), change in sense of taste;
- inflammation of the vagina;
- pain when passing urine;
- if you have previously had skin reactions, i.e., pain, redness and dryness of skin, during treatment with radiotherapy, this may also happen with Caelyx;
- joint pain, decreased or abnormal sensation to stimulation, inflammation of the cornea, redness of the eye, redness of the scrotum may occur with a combination of Caelyx and bortezomib.

When Caelyx is used alone, some of these effects are less likely to occur, and some have not occurred at all.

Uncommon side effects (may affect up to 1 in 100 people)
- confusion;
- inflammation of the veins and formation of blood clots in the veins which could lead to blockage of blood flow to your lungs causing difficulty breathing, chest pain and palpitations.

Very rare side effects (may affect up to 1 in 10,000 people)
- serious skin reactions such as widespread peeling skin, blisters as well as mucous membrane erosion (Stevens-Johnson syndrome/toxic epidermal necrolysis);
- oral cancer may occur when Caelyx is taken for a long time (more than one year).

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

Strategies to prevent and treat hand-foot syndrome include:
- soaking hands and/or feet in basins of cold water when possible (e.g., while watching television, reading, or listening to the radio);
- keeping hands and feet uncovered (no gloves, socks, etc.);
- staying in cool places;
- taking cool baths during hot weather;
- avoiding vigorous exercise that might cause trauma to the feet (e.g., jogging);
- avoiding exposure of skin to very hot water (e.g., jacuzzis, saunas);
- avoiding tight fitting footwear or high-heeled shoes.

Pyridoxine (Vitamin B6):
- vitamin B6 is available without prescription;
- take 50-150 mg daily beginning at the first signs of redness or tingling.

5. How to store Caelyx

Keep this medicine out of the sight and reach of children.

Store in a refrigerator (2°C – 8°C). Do not freeze.

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.

Do not use this medicine after the expiry date which is stated on the label and carton.

Do not use this medicine if you notice that it shows evidence of precipitation or any other particulate matter.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Caelyx contains
- The active substance is doxorubicin hydrochloride. One ml of Caelyx contains 2 mg of doxorubicin hydrochloride in a pegylated liposomal formulation.
- The other ingredients are 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 and sodium hydroxide.

Caelyx concentrate for solution for infusion: vials which provide 10 ml (20 mg) or 25 ml (50 mg).

What Caelyx looks like and contents of the pack
The solution for infusion is sterile, translucent and red. Caelyx is available in glass vials as a single pack or packs of ten vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
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Manufacturer
Janssen Pharmaceutica NV
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last approved on

Detailed information on this medicine is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

The following information is intended for medical or healthcare professionals only (see section 3):

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

Determine the dose of Caelyx to be administered (based upon the recommended dose and the patient's body surface area). Take the appropriate volume of Caelyx up into a sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Caelyx. The appropriate dose of Caelyx must be diluted in 5% (50 mg/ml) glucose solution for infusion prior to administration. For doses < 90 mg, dilute Caelyx in 250 ml, and for doses ≥ 90 mg, dilute Caelyx in 500 ml.

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 Caelyx 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 was 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.

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.

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.

It is recommended that the Caelyx 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.