1 PRODUCT NAME

CAELYX (2mg/mL concentrate for infusion).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of **CAELYX** contains 2mg doxorubicin hydrochloride in a pegylated liposomal formation. Each vial contains 20mg or 50mg doxorubicin hydrochloride.

CAELYX, a pegylated liposomal formulation of doxorubicin hydrochloride, contains doxorubicin encapsulated in liposomes having surface-bound methoxypolyethylene glycol groups (pegylated liposomes). This process is known as pegylation and protects the 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 infusion.

CAELYX is a concentrate for infusion presented as a sterile, translucent, red suspension in glass vials containing 10mL or 25mL for single-use intravenous infusion, with a pH of 6.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CAELYX is indicated for the treatment of:

- Metastatic breast cancer in women for whom an anthracycline would be considered.
- Metastatic breast cancer in women who have failed a taxane-containing regimen.
- Advanced epithelial ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.
- AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (< 200 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 doxorubicin (or other anthracycline).

CAELYX is also indicated, 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.

4.2 Dose 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 HCl.

DOSE

Breast cancer/Ovarian cancer

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

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

To minimise the risk of infusion reactions, the initial dose is administered at a rate no greater than 1mg/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 over the next 15 minutes. If tolerated, the infusion was completed over the next hour for a total infusion time of 90 minutes.

Subsequent **CAELYX** infusions may be administered over a 60-minute period.

Multiple myeloma
CAELYX is administered at 30mg/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 1.3mg/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.

For doses < 90mg: dilute **CAELYX** in 250mL of 5% (50mg/mL) glucose solution for infusion.
For doses ≥ 90mg: dilute **CAELYX** in 500mL of 5% (50mg/mL) glucose solution for infusion.

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

- 10mL over first 10 minutes
- 20mL over next 10 minutes
- 40mL over next 10 minutes
- then, complete the infusion over a total of 90 minutes.

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

- 10mL over first 10 minutes
- 20mL over next 10 minutes
- 40mL over next 10 minutes
- then, complete the remaining infusion over a total of 90 minutes.

Infusion may be given through a peripheral vein or a central line.

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

CAELYX, diluted in 250mL 5% Glucose Intravenous Infusion, is administered by intravenous infusion over 30 minutes.

All patients
If the patient experiences early symptoms or signs of infusion reaction (see section 4.4), 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) (US).

The tables for PPE and stomatitis 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 haematologic 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			
Toxicity Grade at current assessment	Week after prior CAELYX dose		
	Week 4	Week 5	Week 6
Grade 1 (mild erythema, swelling, or desquamation not interfering with daily activities)	Re-dose unless patient has experienced a previous Grade 3 or 4 skin toxicity, in which case wait an additional week	Re-dose 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 2cm in diameter)	Wait an additional week	Wait an additional week	Decrease dose by 25%; return to 4-week interval
Grade 3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	Wait an additional week	Wait an additional week	Discontinue CAELYX
Grade 4 (diffuse or local process causing infectious complications, or a bedridden state or hospitalisation)	Wait an additional week	Wait an additional week	Discontinue CAELYX

Table 2: STOMATITIS			
Toxicity Grade at current assessment	Week after prior CAELYX dose		
	Week 4	Week 5	Week 6
Grade 1 (painless ulcers, erythema, or mild soreness)	Re-dose unless patient has experienced a previous Grade 3 or 4 stomatitis, in which case wait an additional week	Re-dose 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, oedema, or ulcers, but cannot eat)	Wait an additional week	Wait an additional week	Discontinue **CAELYX**
Grade 4 (requires parenteral or enteral support)	Wait an additional week	Wait an additional week	Discontinue **CAELYX**

Table 3: HAEMATOLOGICAL TOXICITY (ANC OR PLATELETS):			
1. MANAGEMENT OF PATIENTS WITH BREAST OR OVARIAN CANCER			
Grade	ANC ($\times 10^9$/L)	PLATELETS ($\times 10^9$/L)	MODIFICATION
Grade 1	1.5 - 1.9	75 - 150	Resume treatment with no dose reduction
Grade 2	1.0 - < 1.5	50 - < 75	Wait until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L; re-dose with no dose reduction
Grade 3	0.5 - < 1.0	25 - < 50	Wait until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L; re-dose with no dose reduction
Grade 4	< 0.5	< 25	Wait until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L; decrease dose by 25% or continue full dose with growth factor support.
2. MANAGEMENT OF PATIENTS WITH AIDS-KS			
	ANC ($\times 10^9$/L)	PLATELETS ($\times 10^9$/L)	**MODIFICATION**
Grade 1	1.5 - 1.9	75 - 150	Resume treatment with no dose reduction
Grade 2	1.0 - < 1.5	50 - < 75	
Grade 3	0.5 - < 1.0	25 - < 50	Wait until ANC ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L; re-dose with no dose reduction. G-CSF (or GM-CSF) may be given as concomitant therapy to support the blood count when the ANC count is < 1 x 10^9/L.
Grade 4	< 0.5	< 25	

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 Table 2 above, respectively. For more detailed information on bortezomib dosing and dosage adjustments, see the Prescribing Information for bortezomib.

Table 4. DOSAGE ADJUSTMENTS FOR CAELYX + BORTEZOMIB COMBINATION THERAPY - PATIENTS WITH MULTIPLE MYELOMA		
Patient Status	CAELYX	Bortezomib
Fever ≥ 38°C and ANC < 1000/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 Haemoglobin < 8g/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 haematologic toxicity.*	Do not dose; if 2 or more doses are not given in a cycle, reduce dose by 25% in following cycles.
Grade 3 or 4 non-haematologic medicine related toxicity	Do not dose until recovered to Grade < 2 and reduce dose by 25% for all subsequent doses.	Do not dose until recovered to Grade < 2 and reduce dose by 25% for all subsequent doses.
Neuropathic pain or peripheral neuropathy	No dosage adjustments.	See the Product Information for bortezomib
* for more information on bortezomib dosing and dosage adjustment, see the Product Information for bortezomib		

Guidelines for CAELYX dose modification

Patients with impaired hepatic function

Prior to **CAELYX** administration, hepatic function should be evaluated using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase and bilirubin. In a small number of patients with impaired hepatic function (bilirubin values up to 70 micromoles/L) administered 20mg/m^2 of **CAELYX**, there appeared to be no change in the clearance and terminal half-life of **CAELYX**. However, until further experience is gained, the **CAELYX** dosage should be reduced in patients with impaired hepatic function, based on experience from the breast and ovarian clinical trial programs as follows:

At initiation of therapy, if the bilirubin is between 20 – 51 micromoles/L, the first dose is reduced by 25%. If the bilirubin is > 51 micromoles/L, 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. No data are available for patients with severe hepatic impairment.

Patients with impaired renal function

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

AIDS-KS patients with splenectomy

As there is no experience with **CAELYX** in patients with splenectomy, treatment with **CAELYX** is not recommended.

Paediatric patients

The safety and effectiveness in patients less than 18 years of age have not been established.

Elderly patients
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.

CAELYX MUST NOT BE GIVEN BY THE INTRAMUSCULAR OR SUBCUTANEOUS ROUTE (see sections 4.4 and 6.6).

DO NOT administer as a bolus injection or undiluted suspension.

For further instructions on preparation of the medicine before administration and special precautions for handling see section 6.6.

4.3 Contraindications

- **CAELYX** is contraindicated in patients who have a history of hypersensitivity reactions to the active substance doxorubicin HCl or to any of the excipients listed in section 6.1.
- **CAELYX** should not be administered during pregnancy or while breast feeding.
- **CAELYX** should 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

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

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

Cardiac risk
Experience with **CAELYX** at high cumulative doses is too limited to have established its effects on the myocardium (see sections 4.4 and 4.8). The long-term cardiac effects of **CAELYX** relative to the conventional formulation of doxorubicin HCl have not been adequately evaluated. Until further clinical data are available, the risk of developing cardiomyopathy is assumed to be similar to that of standard doxorubicin.

All patients receiving **CAELYX** should 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, should be considered.

More specific methods for evaluation and monitoring of cardiac functions as compared to ECG are a measurement of left ventricular ejection fraction by echocardiography or preferably by multiple gated angiography (MUGA). These methods should be applied routinely before the initiation of **CAELYX** and should be repeated periodically during treatment. In a phase-III clinical trial comparing **CAELYX** (50mg/m^2 every 4 weeks) versus doxorubicin (60mg/m^2 every 3 weeks), 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 between 450mg/m^2 and 600mg/m^2 there was no increased risk of cardiac toxicity with **CAELYX**. The evaluation of left ventricular function is considered to be mandatory before each additional dose of **CAELYX** that

exceeds a lifetime cumulative dose of 600mg/m^2 or where a lifetime cumulative dose of 450mg/m^2 of other anthracyclines has been administered.

In the multiple myeloma study, LVEF decrease was defined as an absolute decrease of ≥ 15% over baseline or a ≥ 5% decrease below the institutional lower limit of normal. Based on this definition, 25 patients in the bortezomib arm (8 %) and 42 patients in the **CAELYX** plus bortezomib arm (13%) experienced a reduction in LVEF.

The evaluation tests and methods mentioned above concerning the monitoring of cardiac performance during anthracycline therapy should 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. Caution should be exercised 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 should be observed in patients who have received other anthracyclines. The total dose of doxorubicin HCl should 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 450mg/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 (50mg/m^2) is similar to the 20mg/m^2 profile in patients with AIDS-KS.

Myelosuppression

Many patients treated with **CAELYX** have baseline myelosuppression due to such factors as their 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 50mg/m^2, myelosuppression was generally mild to moderate, reversible, and was not associated with episodes of neutropenic 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 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 should be performed frequently during the course of **CAELYX**, and at a minimum, prior to each dose of **CAELYX**.

Persistent myelosuppression, although not seen in patients with breast or ovarian cancer, 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.

In the pivotal multiple myeloma study, myelosuppression (all grades) occurred more frequently in the **CAELYX** plus bortezomib group, compared to bortezomib monotherapy. While the incidence of anaemia was similar for both treatment groups, Grade 3 or 4 neutropaenia and thrombocytopaenia occurred more frequently in the **CAELYX** plus bortezomib group (see section 4.8).

Combination therapy with **CAELYX** has been extensively studied in solid tumour populations. **CAELYX** has been safely co-administered with standard doses of chemotherapeutic agents that are frequently used in the treatment of advanced breast cancer or ovarian cancer, however the efficacy of such combination regimens has not been established.

Infusion-associated reactions
Serious and sometimes life-threatening infusion reactions, which are characterised by allergic-like or anaphylactoid-like reactions, may occur within minutes of starting the infusion of **CAELYX**. Symptoms include asthma, flushing, urticarial rash, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial oedema, chills, headache, 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 1mg/minute (see section 4.2).

Palmar-plantar erythrodysesthesia (Hand-foot syndrome)
Palmar-plantar erythrodysesthesia (PPE) is characterised by painful, red macular and/or papular bullous skin eruptions. In patients experiencing this event, it is generally seen after two or three cycles of treatment. In most patients it clears in one or two weeks, with or without treatment with corticosteroids. Pyridoxine at a dose of 50 - 150mg per day has been used for the prophylaxis and treatment of PPE. Other strategies to prevent and treat PPE include keeping hands and feet cool, by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight-fitting). It appears to be dose- and schedule-related and can be reduced by extending the **CAELYX** dose interval 1 - 2 weeks or reducing the **CAELYX** dose (see section 4.2). This reaction can be severe and debilitating in some patients, however, and may require discontinuation of treatment.

Extravasation injury
Although local necrosis following extravasation has been reported very rarely, **CAELYX** should be considered an irritant. Although animal studies indicate that the administration of doxorubicin HCl as a liposomal formulation reduces the potential for extravasation injury, the possibility of doxorubicin-related skin injury exists, and care should be taken to avoid extravasation of **CAELYX**. If any signs or symptoms of extravasation occur (e.g. stinging, erythema) the infusion should be immediately terminated and restarted 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.

Radiation recall reaction
Recall of skin reaction due to prior radiotherapy has rarely occurred with **CAELYX** administration.

Diabetic patients
It should be noted that each vial of **CAELYX** contains sucrose and is administered in 5% Glucose Intravenous Infusion.

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 720mg/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.

Interstitial lung disease (ILD)
Interstitial lung disease (ILD), which may have an acute onset, has been observed in patients receiving **CAELYX** (see section 4.8). If patients experience worsening of respiratory symptoms such as dyspnea, dry cough, and fever, **CAELYX** should be interrupted, and the patient should be promptly investigated. If ILD is confirmed, **CAELYX** should be discontinued, and the patient treated appropriately.

Use in hepatic impairment
Please see section 4.2. Patients with impaired hepatic function.

Use in the elderly
No data available.

Paediatric use
No data available.

Effects on laboratory tests
No data available.

4.5 Interaction with other medicines and other forms of interaction

No formal drug interaction studies have been conducted with **CAELYX**, although phase II combination trials with conventional chemotherapy agents have been conducted in patients with gynaecological malignancies. Caution should be exercised in the concomitant use of drugs known to interact with doxorubicin HCl. Although not formally studied, **CAELYX**, like other doxorubicin HCl preparations, may potentiate the toxicity of other anti-cancer therapies.

In patients with solid tumours (including breast and ovarian cancer) who received concomitant cyclophosphamide or taxanes, no new additive toxicities were noted. In patients with AIDS- KS, exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with doxorubicin HCl. Caution should be exercised when giving any other cytotoxic agents, especially myelotoxic agents, at the same time.

4.6 Fertility, pregnancy and lactation

Effects on fertility

CAELYX resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 and 12mg/kg, respectively. Decreased testicular weights and hypospermia were present in rats after repeat doses of 0.25mg/kg/day given once every 3 days, and in rabbits of 1mg/kg given once every 5 days. Diffuse degeneration of the seminiferous epithelium was observed in dogs after 10 doses of 0.25mg/kg given once every 21 days.

Use in pregnancy

Category D. **CAELYX** is embryotoxic at doses of 1mg/kg/day in rats (about 1/3 the recommended human dose on a mg/m^2 basis). **CAELYX** is embryotoxic and abortifacient at 0.5mg/kg/day in rabbits (about 1/4 the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterised by increased embryo-foetal deaths and reduced litter sizes.

There are no adequate and well-controlled studies in pregnant women. If **CAELYX** is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the foetus and such treatment should only proceed with the patient's complete informed consent.

Women of childbearing potential/contraception in men and women

Women of childbearing potential should be advised to avoid pregnancy and use effective contraception while they are receiving **CAELYX** and in the eight months following discontinuation of **CAELYX** therapy.

Men with female partners of childbearing potential should be advised to use effective contraception and should not father a child while receiving **CAELYX** and for up to six months following completion of treatment.

Breast-feeding

It is not known whether this drug is excreted in human milk and because of the potential for serious adverse reactions in nursing infants from **CAELYX**, mothers should discontinue nursing prior to taking this drug. Health experts recommend that HIV-infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

Although **CAELYX** should not affect driving performance, in studies to date, dizziness and somnolence were associated infrequently (< 5%) with the administration of **CAELYX**. Patients who suffer from these effects should avoid driving and operating machinery.

4.8 Undesirable effects

Breast cancer patients (dosage: 50mg/m^2)

254 patients with advanced breast cancer who had not received prior chemotherapy for metastatic disease were treated with **CAELYX** at a dose of 50mg/m^2 every 4 weeks in a phase III clinical trial (I97-328). The most frequently reported treatment related adverse effects included palmar-plantar erythrodysesthesia (PPE) (48.0%) and nausea (37.0%) (see Table 5). Severe (Grade III) cases reported in 17.0% and 3.0% respectively, and no reported incidences of life threatening (Grade IV) cases for either PPE or nausea. These effects resulted in permanent treatment discontinuation (7.0% and 0% respectively). Pronounced alopecia (or total hair loss) was seen in only 7.0% of **CAELYX**-treated patients as compared with 54.0% of patients treated with doxorubicin.

Haematologic adverse effects were infrequently reported and were mostly mild or moderate in severity and manageable. Anaemia, neutropenia, leucopenia and thrombocytopenia were infrequently reported at incidences of 5.0%, 4.0%, 2.0%, and 1.0%, respectively. Life threatening (Grade IV) haematologic effects were reported at incidences of < 1.0%. The need for either growth factor support or transfusion support was minimal (5.1% and 5.5% of patients, respectively).

Clinically significant laboratory abnormalities (Grades III and IV) in this breast cancer group included increases in total bilirubin (2.4%) and AST (1.6%). Increases in ALT were less frequent (< 1%). Clinically significant haematologic measurements were infrequent as measured by leucopenia (4.3%), anaemia (3.9%), neutropenia (1.6%) and thrombocytopenia (1.2%). Sepsis was reported at an incidence of 1%. No clinically significant increases in serum creatinine were reported.

Table 5. MOST FREQUENTLY REPORTED TREATMENT RELATED ADVERSE EFFECTS IN PATIENTS TREATED WITH CAELYX OR DOXORUBICIN

Trial Reference I97-328	Percentage of patients			
	CAELYX		Doxorubicin	
	All Grades	Grades III & IV	All Grades	Grades III & IV
PPE	48	17	2	0
Nausea	37	3	53	5
Mucositis	23	4	13	2
Stomatitis	22	5	15	2
Alopecia	20	0	66	0
Vomiting	19	< 1	31	4
Fatigue	12	< 1	16	2
Anorexia	11	1	10	< 1
Asthenia	10	1	13	1
Rash	10	2	2	0
Abdominal pain	8	1	4	1
Constipation	8	< 1	9	< 1
Pigmentation abnormal	8	< 1	2	< 1
Fever	8	0	7	1
Diarrhoea	7	1	8	< 1
Erythema	7	< 1	1	0
Weakness	6	< 1	8	0
Mouth ulceration	5	< 1	4	0
Anaemia	5	1	7	< 1
Neutropaenia	4	1	10	4

In 150 patients with advanced breast cancer who had failed a prior first- or second-line taxane-containing chemotherapy regimen and were subsequently treated with **CAELYX** at a dose of 50mg/m^2 every 4 weeks in a phase III clinical trial (C/I96-352), the safety profile (see Table 6 below) was consistent with that reported for **CAELYX** in previous studies using the same dosage regimen. The proportion of patients experiencing clinically significant laboratory abnormalities was low and comparable numerically to the 254 breast cancer patients receiving **CAELYX** as first-line therapy, with the exception of leucopenia (20%).

Table 6. FREQUENCY OF TREATMENT-RELATED ADVERSE EFFECTS REPORTED IN PATIENTS TREATED WITH CAELYX VS. VINORELBINE OR MITOMYCIN C + VINBLASTINE

Astudy Reference C/I96-352	Percentage of patients					
	CAELYX		Vinorelbine		Mitomycin + Vinblastine	
	All Grades	Grades III & IV	All Grades	Grades III & IV	All Grades	Grades III & IV
PPE*	37	19	< 1	0	0	0
Nausea	31	3	27	7	23	5
Mucositis	14	3	< 1	0	5	0
Stomatitis	22	5	4	0	0	0
Alopecia	3	0	5	< 1	0	0
Vomiting	19	4	17	3	18	0
Fatigue	20	4	21	2	9	5
Anorexia	11	0	14	< 1	0	0
Asthenia	9	1	15	4	32	0
Rash	15	2	0	0	0	0
Abdominal pain	4	< 1	11	< 1	9	0
Constipation	5	0	16	2	5	0
Fever	4	< 1	12	2	9	5
Diarrhoea	10	< 1	9	0	5	0
Erythema	6	2	2	< 1	0	0
Neutropaenia	3	2	14	8	5	0
Pain	4	1	13	3	5	5
Neuropathy	1	0	11	< 1	5	0
Dyspepsia	5	0	6	0	9	0
Paraesthesia	3	0	9	< 1	5	0
Dyspnoea	6	3	< 1	0	5	0
Headache	4	1	5	0	0	0
Flushing	5	< 1	0	0	0	0
Weight decrease	5	0	2	< 1	0	0
Pruritis	5	0	< 1	0	0	0
Phlebitis	< 1	< 1	7	2	0	0
Injection site pain	0	0	5	2	0	0
Hypoaesthesia	< 1	0	5	0	0	0
Myalgia	0	0	5	0	0	0
Moniliasis	1	0	2	0	9	0
Skin discolouration	5	< 1	0	0	0	0

* Palmar-plantar erythrodysesthesia (Hand-foot syndrome). One case of Grade IV (life threatening) PPE was reported in C/I96-352, no cases were reported in I97-328.

Adverse effects reported between 1% and 5% in 404 **CAELYX**-treated breast cancer patients, not previously reported in **CAELYX** clinical trials (≥ 1%) were breast pain, leg cramps, oedema, leg oedema, peripheral neuropathy, oral pain, ventricular arrhythmia, folliculitis, bone pain, musculo-skeletal pain, thrombocythemia, cold sores (non-herpetic), fungal infection, epistaxis, upper respiratory tract infection, bullous eruption, dermatitis, erythematous rash, nail disorder, scaly skin, lacrimation, and blurred vision.

A 12.4% incidence of infusion-related adverse events was observed in pivotal breast cancer trials. Permanent treatment discontinuation was reported at 1.5%.

Ovarian cancer patients (dosage: 50mg/m^2)

Based on the experience in 512 patients with ovarian cancer treated at a dose of 50mg/m^2, the frequency of adverse events reported in clinical trials is listed below and classified according to body systems:

Cardiovascular

Common (≥ 1% and < 10%):	Cardiovascular disorder, vasodilatation, cardiac toxicity (see *All Patients*).
Uncommon (≥ 0.1% and < 1%):	Palpitation.

Dermatological

Very Common (≥ 10%):	Palmar-plantar erythrodysesthesia (PPE), rash, alopecia.
Common (≥ 1% and < 10%):	Skin discolouration, dry skin, pruritus, vesiculobullous rash, skin disorder, exfoliative dermatitis, maculopapular rash, acne, skin ulcer.
Uncommon (≥ 0.1% and < 1%):	PPE (Grade IV - life threatening), nail disorder.

The overall incidence of PPE was very common at 46.1%. This comprised, in decreasing order of frequency, Grade III (severe) 19.5%, Grade II (Moderate) 16.4%, Grade I (Mild) 9.6%, and Grade IV (life threatening) 0.6%.

Gastrointestinal

Very Common (≥ 10%):	Stomatitis, nausea, vomiting, constipation, diarrhoea, anorexia.
Common (≥ 1% and < 10%):	Stomatitis (Grade III - severe), abdominal pain, dyspepsia, weight loss, oesophagitis, gastritis, dysphagia, mouth ulceration, nausea and vomiting, oral moniliasis, gingivitis, flatulence, dry mouth, hyperbilirubinemia (usually in patients with liver metastases).
Uncommon (≥ 0.1% and < 1%):	Stomatitis (Grade IV - life threatening), increased AST.

Haematological

Very Common (≥ 10%):	Anaemia (32.2%), leucopenia (33.2%), neutropenia (31.6%), thrombocytopenia (10.7%).
Common (≥ 1% and < 10%):	Neutropenia (Grade IV - life threatening) (2.9%), leucopenia (Grade IV - life threatening) (1.6%), hypochromic anaemia.
Uncommon (≥ 0.1% and < 1%):	Anaemia (Grade IV - life threatening) (0.4%), thrombocytopenia (Grade IV - life threatening) (0.2%), sepsis related to leucopenia.

In the 512 patients with ovarian cancer treated at a dose of 50mg/m^2, myelosuppression was mostly mild or moderate and manageable. Growth factor was required infrequently (< 5%) and transfusion support was required in approximately 15% of the patients (see section 4.2).

Musculoskeletal

Common (≥ 1% and < 10%):	Myalgia.

Neurological

Common (≥ 1% and < 10%):	Paraesthesia, somnolence, dizziness, depression, insomnia, anxiety, neuropathy.
Uncommon (≥ 0.1% and < 1%):	Peripheral neuritis.

Ocular

Common (≥ 1% and < 10%):	Conjunctivitis.
Uncommon (≥ 0.1% and < 1%):	Amblyopia.

Respiratory

Common (≥ 1% and < 10%):	Dyspnoea, increased cough, pharyngitis.
Uncommon (≥ 0.1% and < 1%):	Rhinitis.

Urogenital

Common (≥ 1% and < 10%):	Urinary tract infection, dysuria, vaginitis, increased serum creatinine.

General

Very Common (≥ 10%):	Asthenia, mucous membrane disorder, infusion reactions.
Common (≥ 1% and < 10%):	Fever, pain, headache, peripheral oedema, allergic reaction, dehydration, chills, infection, chest pain, back pain, malaise, sweating, taste perversion, herpes zoster, cachexia, hypertonia.
Uncommon (≥ 0.1% and < 1%):	Enlarged abdomen, facial oedema.

Multiple myeloma patients (dosage: 30mg/m^2)

Of 646 patients with multiple myeloma who have received at least 1 prior therapy, 318 patients were treated with combination therapy of **CAELYX** 30mg/m^2 as a one-hour intravenous infusion administered on day 4 following bortezomib, which is administered at 1.3mg/m^2 on days 1, 4, 8 and 11, every three weeks or with bortezomib monotherapy in a phase III clinical trial.

In both treatment groups, the median number of cycles received was 5, and the median duration was 105 days. The mean and median cycle lengths were similar between the two groups and consistent with the protocol of 21 days. Monotherapy patients received 24.4mg/m^2 mean cumulative bortezomib dose compared with 23.3mg/m^2 in the combination therapy group. The median of the mean **CAELYX** dose per patient was 29.83mg/m^2/day.

Treatment discontinuation of one or both agents in the combination therapy group occurred in 38% of patients, compared to 24% of patients in the monotherapy group. Common adverse events that led to treatment discontinuation of bortezomib and **CAELYX** included PPE, neuralgia, peripheral neuropathy, peripheral sensory neuropathy, thrombocytopaenia, decreased ejection fraction, and fatigue.

See Table 7 for treatment-related adverse effects reported in ≥ 2% of patients treated with combination therapy of **CAELYX** plus bortezomib or bortezomib alone.

The combination therapy was associated with a higher incidence of Grade 3 or 4 myelosuppression, constitutional symptoms, and GI and dermatologic toxicities. Grade 3 or 4 adverse drug reactions were more frequent in the combination therapy group (68% vs. 52%). This was mostly due to an increase in Grade 3 or 4 haematologic or Grade 3 GI adverse events. Neutropaenia, thrombocytopaenia, and anaemia were the most frequently reported haematologic 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 Grade 3 and 4 anaemia was similar in both treatment groups (7% vs. 5%).

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.

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.

The most frequently reported treatment-related adverse events in combination therapy were nausea (40%), diarrhoea (35%), neutropaenia (33%), thrombocytopaenia (29%), vomiting (28%), fatigue (27%), and constipation (22%). PPE was reported in 16% of multiple myeloma patients treated with combination therapy. Grade 3 PPE was reported in 5% of patients. No Grade 4 PPE was reported.

Table 7. FREQUENCY OF TREATMENT-RELATED ADVERSE EFFECTS REPORTED IN AT LEAST 2% OF SUBJECTS TREATED FOR MULTIPLE MYELOMA (STUDY CAELYX-MMY-3001: SAFETY ANALYSIS SET)

Adverse Reaction	VELCADE (bortezomib) (N = 318)			VELCADE + CAELYX (N = 318)		
	Any (%)	Grade 3 (%)	Grade 4 (%)	Any (%)	Grade 3 (%)	Grade 4 (%)
Blood and lymphatic system disorders						
Neutropaenia	20	10	4	33	20	8
Thrombocytopaenia	24	7	7	29	11	11
Anaemia	13	5	< 1	18	6	1
Leukopaenia	6	2	< 1	8	3	2
Febrile neutropaenia	1	< 1	0	3	2	< 1
Lymphopaenia	1	< 1	0	2	< 1	< 1
Ear and labyrinth disorders						
Vertigo	2	1	< 1	1	< 1	0
Eye disorders						
Conjunctivitis	1	0	0	3	0	0
Vision blurred	2	0	0	1	0	0
Gastrointestinal disorders						
Nausea	32	< 1	0	40	2	0
Diarrhoea	27	4	0	35	7	0
Vomiting	15	< 1	0	28	4	0
Constipation	19	< 1	0	22	1	0
Stomatitis	3	< 1	0	16	2	0
Abdominal pain	4	1	0	7	< 1	0
Dyspepsia	2	0	0	5	< 1	0
Abdominal pain upper	1	0	0	4	1	0
Dry mouth	< 1	0	0	2	0	0
Dysphagia	< 1	0	0	2	0	0
General disorders and administration site conditions						
Fatigue	22	2	0	27	5	< 1
Pyrexia	14	< 1	0	18	1	0
Asthenia	11	2	0	16	5	0
Oedema peripheral	5	0	0	4	0	0
Chills	5	0	0	4	0	0
Influenza like illness	2	0	0	3	< 1	0
Malaise	1	0	0	3	0	0
Pain	3	< 1	0	1	< 1	0
Hyperthermia	0	0	0	2	< 1	0

Infections and infestations						
Herpes simplex	3	< 1	0	8	0	0
Herpes zoster	4	1	0	6	1	0
Pneumonia	3	2	1	3	2	< 1
Upper respiratory tract infection	2	< 1	0	4	< 1	0
Nasopharyngitis	1	0	0	3	0	0
Lower respiratory tract infection	2	< 1	0	1	< 1	0
Investigations						
Weight decreased	3	0	0	8	0	0
Aspartame aminotransferase increased	2	0	0	3	0	0
Ejection fraction decreased	0	0	0	3	0	0
Blood creatinine increased	1	0	0	2	0	0
Metabolism and Nutritional disorders						
Anorexia	10	0	0	16	1	0
Decreased appetite	2	0	0	8	< 1	0
Dehydration	2	1	0	3	< 1	0
Hypokalaemia	1	0	< 1	3	1	< 1
Hyperkalaemia	1	< 1	0	2	< 1	0
Hypomagnesaemia	1	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	6	< 1	0	5	0	0
Arthralgia	4	< 1	0	4	< 1	0
Myalgia	4	< 1	0	3	0	0
Bone pain	3	< 1	0	1	< 1	0
Muscle spasms	1	0	0	2	0	0
Muscular weakness	1	0	0	2	0	0
Musculoskeletal pain	2	0	0	1	0	0
Back pain	2	< 1	0	1	< 1	0
Nervous system disorders						
Neuralgia	15	4	< 1	14	3	0
Peripheral sensory neuropathy	11	2	0	10	1	0
Peripheral neuropathy	12	3	< 1	9	2	0
Neuropathy	10	1	0	8	1	0
Headache	9	0	0	10	< 1	< 1
Paraesthesia	6	0	0	9	< 1	0
Polyneuropathy	8	2	1	6	0	0
Dizziness	4	1	< 1	6	1	0
Dysgeusia	2	0	0	5	0	0
Lethargy	3	0	0	3	< 1	0
Hypoaesthesia	3	0	0	2	0	0
Peripheral motor neuropathy	2	< 1	0	1	< 1	0
Psychiatric disorders						
Insomnia	5	0	< 1	5	0	0
Anxiety	1	0	0	2	< 1	0

Respiratory, thoracic and mediastinal disorders						
Dyspnoea	3	1	< 1	5	< 1	0
Cough	2	0	0	3	0	0
Epistaxis	1	< 1	0	2	< 1	0
Pharyngolaryngeal pain	2	0	0	1	0	0
Dyspnoea exertional	< 1	0	0	2	< 1	0
Skin and subcutaneous tissue disorders						
Hand-foot syndrome	0	0	0	16	5	0
Rash	6	< 1	0	11	< 1	0
Dry skin	1	0	0	5	0	0
Pruritus	3	< 1	0	3	< 1	0
Rash popular	2	0	0	3	0	0
Dermatitis allergic	2	< 1	0	1	0	0
Erythema	1	0	0	3	0	0
Skin hyperpigmentation	0	0	0	3	0	0
Rash erythematous	2	< 1	0	1	0	0
Petechiae	1	0	0	2	0	0
Alopecia	< 1	0	0	2	0	0
Urticaria	2	< 1	0	< 1	0	0
Drug Eruption	0	0	0	2	0	0
Vascular disorders						
Hypotension	3	< 1	0	4	1	0
Orthostatic hypotension	2	< 1	0	3	< 1	0
Flushing	< 1	0	0	2	0	0

Other adverse effects reported in ≥ 1% but < 2% of **CAELYX** and bortezomib combination therapy - treated patients are mouth ulceration, oral candidiasis, aphthous stomatitis, alanine amino-transferase increased, hyponatraemia, hypocalcaemia, musculoskeletal chest pain, syncope, dysaesthesia, scrotal erythema, hypertension and phlebitis.

The incidence of treatment-related heart dysfunction events (ventricular dysfunction, cardiac failure, right ventricular failure, congestive cardiac failure, chronic cardiac failure, acute pulmonary oedema and pulmonary oedema) was similar - 1% and 2% in the monotherapy and combination therapy, respectively.

In AIDS-KS patients (dosage: 20mg/m^2)

CAELYX has been evaluated for safety in 825 AIDS-KS patients treated in 5 clinical trials. Myelosuppression was the most prevalent side effect considered related to **CAELYX** treatment occurring in approximately half of the patients.

Cardiovascular

Uncommon (≥ 0.1% and < 1%):	Congestive heart failure, cardiomyopathy and cardiotoxicity (see All Patients).

Gastrointestinal

Very common (≥ 10%):	Nausea.
Common (≥ 1% and < 10%):	Abdominal pain, anorexia, constipation, diarrhoea, glossitis, mouth ulceration, oral moniliasis, nausea and vomiting, vomiting, weight loss, stomatitis, increased alkaline phosphatase, increased AST and hyperbilirubinemia (believed to be disease-related).

Haematological

Very common (≥ 10%):	Leucopenia, anaemia.
Common (≥ 1% and < 10%):	Thrombocytopenia, laboratory abnormalities.
Uncommon (≥ 0.1% and < 1%):	Sepsis related to leucopenia.

Leucopenia is the most common adverse event experienced with **CAELYX** in this population; and can occur during all cycles of administration of **CAELYX**. In clinical trials, patients rarely discontinued treatment due to myelosuppression. Haematological toxicity may require dose reduction or suspension or delay of therapy (see section 4.2). The haematological toxicity for ovarian cancer patients is less severe than in the AIDS-KS setting (see section for ovarian cancer patients above).

Dermatological

Common (≥ 1% and < 10%):	Alopecia, palmar-plantar erythrodysesthesia, rash.
Rare (≥ 0.01% and < 0.1%):	Recall of skin reaction due to prior radiotherapy has rarely occurred with **CAELYX** administration.

Respiratory

Very common (≥ 10%):	Opportunistic infections (may be related to HIV-induced immunodeficiency). The most frequently observed OI's in clinical studies were candidiasis, cytomegalovirus, herpes simplex, *Pneumocystis carinii pneumonia* and *Mycobacterium avium* complex.
Common (≥ 1% and < 10%):	Dyspnoea.

Ocular

Common (≥ 1% and < 10%):	Retinitis.

General

Very Common (≥ 10%):	Asthenia.
Common (≥ 1% and < 10%):	Allergic reaction, fever, paraesthesia, vasodilatation, infusion-associated reactions characterised by flushing, shortness of breath, facial oedema, headache, chills, back pain, tightness in the chest and throat and/or hypotension.
Uncommon (≥ 0.1% and < 1%):	Anaphylactoid reactions, convulsion, tumour necrosis.

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 drug interaction. Permanent treatment discontinuation rates were infrequently reported at 2%. Very rarely, convulsions have been observed in relation to infusion reactions. In patients with multiple myeloma receiving **CAELYX** plus bortezomib, infusion-associated reactions have been reported at a rate of 3%. In all patients, infusion-related reactions occurred primarily during the first infusion (see section 4.4).

Myelosuppression associated with anaemia, thrombocytopenia, leucopenia, and rarely febrile neutropenia, has been reported in **CAELYX**-treated patients.

Endomyocardial biopsies on nine of ten AIDS-KS patients receiving cumulative doses of **CAELYX** greater than 460mg/m^2 indicate no evidence of anthracycline-induced cardiomyopathy. However, until further clinical data are available, the risk of developing cardiomyopathy is assumed to be similar to that of standard doxorubicin. The recommended dose of **CAELYX** for AIDS-KS patients is

20mg/m^2 every two to three weeks. The cumulative dose at which cardiotoxicity would become a concern (> 400mg/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 (including patients with ovarian or breast cancer) with cumulative anthracycline doses of 509mg/m^2 – 1680mg/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, 10/254 patients randomized to receive **CAELYX** (treated at a dose of 50mg/m^2 every 4 weeks) versus 48/255 patients randomised to receive doxorubicin (treated at a dose of 60mg/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). Patients were also assessed for signs and symptoms of congestive heart failure (CHF). None of the 10 **CAELYX** patients who had cardiac toxicity by LVEF criteria developed signs and symptoms of CHF. In contrast, 10 of 48 doxorubicin patients 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 50mg/m^2/cycle with lifetime cumulative anthracycline doses up to 1532mg/m^2, the incidence of clinically significant cardiac dysfunction was low. Of the 929 patients treated with **CAELYX** 50mg/m^2/cycle, baseline measurement of left ventricular ejection fraction (LVEF) and at least one follow-up measurement were conducted in 418 patients and assessed by MUGA scan. Of these 418 patients, 88 patients had a cumulative anthracycline dose of > 400mg/m^2, an exposure level associated with an increased risk of cardiovascular toxicity with the conventional formulation of 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 (who received a cumulative dose of 944mg/m^2), discontinued study treatment because of clinical symptoms of congestive heart failure.

Post-marketing

Adverse reactions identified during the post-marketing experience with **CAELYX** are described below. The frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000, < 1/1000
Very rare	< 1/10000, including isolated reports.

Skin and subcutaneous tissue disorders

Following the marketing of **CAELYX**, serious skin conditions including erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis and lichenoid keratosis have been reported very rarely.

Vascular disorders

Patients with cancer are at increased risk for thromboembolic disease. In patients treated with **CAELYX**, cases of thrombophlebitis and venous thrombosis are seen uncommonly, as well as rare cases of pulmonary embolism.

Respiratory, thoracic and mediastinal disorders
Interstitial lung disease.

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 720mg/m^2 (see section 4.4).

Secondary acute myeloid leukemia and myelodysplastic syndrome
As with other DNA damaging antineoplastic agents, secondary acute myeloid leukemia and myelodysplastic syndrome have been reported rarely in patients having received combined treatment with doxorubicin.

Renal and urinary disorders
Cases of Renal-limited thrombotic microangiopathy have been reported in patients with high cumulative exposure to pegylated liposomal doxorubicin.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

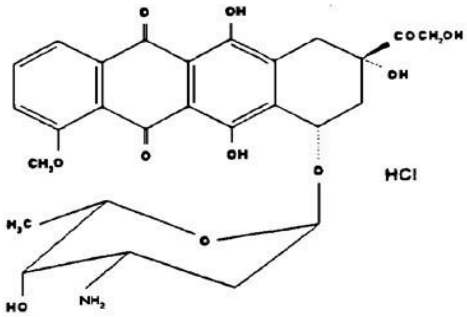
4.9 Overdose
Acute overdosage with doxorubicin HCl worsens the toxic effects of mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage of the severely myelosuppressed patient consists of hospitalisation, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on: 0800 POISON [0800764 766].

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic groups
Cytotoxic agents (anthracyclines and related substances).

ATC codes
L01DB01.

Physicochemical properties
The chemical structure of doxorubicin hydrochloride is:



CAS Registry Number: 25316-40-9.

Mechanism of action

The active ingredient of **CAELYX** is doxorubicin HCl, a cytotoxic anthracycline antibiotic. The exact mechanism of the anti-tumour 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 effect. 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 studies

Breast cancer

A phase III randomized study of **CAELYX** versus doxorubicin hydrochloride 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 (see Table 8), the treatment hazard ratio (HR) for progression-free survival (PFS) when adjusted for prognostic variables was consistent with PFS for the ITT population.

Table 8: CAELYX VS. DOXORUBICIN HYDROCHLORIDE IN METASTATIC BREAST CANCER			
Study I97-328	CAELYX	Doxorubicin	Hazard Ratio (95% CI)
No. of patients	254	255	
Median Progression-Free Survival (months)	6.9	7.8	1.00 (0.82 – 1.22)
Medial Overall Survival (months)	21	22	0.94 (0.74 – 1.19)
Overall Response Rate	33%	38%	

301 patients with advanced breast cancer who had failed a taxane-containing regimen were randomized in a phase III comparative study to **CAELYX** versus an approved salvage regimen (vinorelbine or mitomycin C + vinblastine). Progression-free survival (PFS) was similar for **CAELYX** and the active comparator.

Table 9: CAELYX VS. VINORELBINE OR MITOMYCIN C + VINBLASTINE IN ADVANCED BREAST CANCER			
Study I96-352	CAELYX	Vinorelbine or Mitomycin C + Vinblastine	Hazard Ratio (95% CI)
No. of patients	150	151	
Median Progression-Free Survival (months)	2.9	2.5	1.26 (0.98 – 1.62) p = 0.11
Medial Overall Survival (months)	10.4	9.0	1.07 (0.79 – 1.45)
Overall Response Rate	9%	11%	

Ovarian cancer

CAELYX was compared to topotecan in a randomised, open-label trial in 474 patients with epithelial ovarian cancer after platinum-based chemotherapy. The median age of patients was 60 years (range 25 - 87). Approximately half the patients were platinum-sensitive, defined as response to initial platinum-based therapy and a progression-free interval of greater than 6 months off treatment.

The **CAELYX** dose was 50mg/m^2 infused intravenously over one hour every 4 weeks and the topotecan dose 1.5mg/m^2 infused intravenously daily for 5 consecutive days every 3 weeks. The median duration of follow up was 56.3 months (range 49.9 - 71.5) for **CAELYX**, and 56.5 months (range 49.9 - 72.0) for topotecan.

CAELYX was at least equivalent to topotecan in time to disease progression and survival (Table 10):

Table 10: OVARIAN CANCER TRIAL			
	CAELYX n = 240 randomised	Topotecan n = 241 randomised	Hazard Ratio (95% CI)
ITT	n = 239	n = 235	
Time to Progression (mths median)	4.1	4.2	0.95 [0.76, 1.19]
Overall Survival (mths median)	14.5	13.8	0.82 [0.68, 1.00]
ITT: patients who received at least a partial dose of study drug. Hazard ratio < 1 indicates an advantage for CAELYX. Criterion for non-inferiority: upper limit of 95% CI of Hazard Ratio < 1.3			

CAELYX was also at least equivalent to topotecan in the 4 predefined subgroups, platinum-sensitive, platinum-refractory, tumour size ≤ 5cm and tumour size > 5cm.

CAELYX-treated patients had similar health-related quality-of-life scores assessed by the EORTC QLQ-C30 questionnaire as topotecan-treated patients. However, over the period of 15 months following randomisation, patients treated with **CAELYX** had an average of 1.1 months longer without disease symptoms or Grade 3 - 4 drug toxicity (TWiST) compared with topotecan-treated patients, 95% CI [0.5, 1.8].

Multiple myeloma

A phase III randomised, parallel-group, open-label, multi-centre study was conducted in 646 patients with multiple myeloma, comparing the safety and efficacy of **CAELYX** plus bortezomib combination therapy with bortezomib monotherapy. Patients had not previously received bortezomib, and had disease which progressed during or after at least one prior therapy. All subjects received prior therapies, and 56% had undergone stem cell transplantation.

In both treatment groups bortezomib 1.3mg/m^2 was administered as an IV bolus on Days 1, 4, 8 and 11 every 21 days. In the combination therapy arm **CAELYX** 30mg/m^2 was administered as an infusion after bortezomib on Day 4 of each cycle.

The primary endpoint was time to progression (TTP), defined as the time from randomisation to the first occurrence of progressive disease or death due to progressive disease. The median TTP was 6.5 months for bortezomib monotherapy treated patients compared to 9.3 months for **CAELYX** plus bortezomib combination therapy treated patients ($p < 0.0001$), which triggered protocol-defined early study termination for efficacy. This planned interim analysis was performed with a total of 249 subjects with TTP events (39% of ITT population).

The secondary endpoints for overall survival and response rate were assessed at the interim analysis. Survival data were not mature, and were not statistically significant, although there was a trend of overall survival benefit for **CAELYX** plus bortezomib treated patients (HR 1.48, 95% CI 0.91 – 2.41). Overall response rates were not significantly different between treatment groups. See Table 11 below.

Table 11: EFFICACY OF CAELYX PLUS BORTEZOMIB IN TREATMENT OF PATIENTS WITH MULTIPLE MYELOMA		
Endpoint	CAELYX + bortezomib, n = 324	Bortezomib, n = 322
Time to Progression [a]		
Progression or death due to progression (n)	99	150
Censored (n)	225	172
Median in days (months)	282 (9.3)	197 (6.5)
95% CI	250; 338	170; 217
Hazard ratio [b]	0.55	
(95% CI)	(0.43; 0.71)	
p-value [c]	< 0.0001	
Response (n) [d]	303	310
% Complete Response (CR)	5	3
% Partial Response (PR)	43	40
% CR + PR	48	43
p-value [e]	0.251	
Median Duration of Response (months)	10.2	7.0
(95 % CI)	(10.2; 12.9)	(5.9; 8.3)

a Kaplan Meier estimate

b Hazard ratio based on stratified Cox proportional hazards regression. A hazard ratio < 1 indicates an advantage of CAELYX + bortezomib.

c Stratified log-rank test.

d RR as per EBMT criteria

e Cochran-Mantel-Haenszel test adjusted for the stratification factors.

AIDS-KS

Five clinical studies in patients with AIDS-KS were evaluated. The primary study was conducted in 258 patients and was an open, randomised comparative study comparing the efficacy and safety of **CAELYX** (133 patients) versus adriamycin, bleomycin and vincristine (ABV, 125 patients). The other studies, which provide supportive data, were open, non-randomised studies of the use of **CAELYX** for the treatment of AIDS-related KS.

In the primary study, **CAELYX** was administered at a dose of 20mg/m^2 by intravenous infusion every 2 weeks. The doses of ABV were adriamycin 20mg/m^2, bleomycin 10U/m^2 and vincristine 1.0mg every 2 weeks. Both treatment arms were to continue for a maximum of 6 cycles of treatment. The two groups were well matched for age, sex, weight, prior chemotherapy, HIV risk factor, immune status and severity of KS. All patients were assessed for tumour burden, immune competence and systemic illness factors using the AIDS Clinical Trials Group criteria for staging KS. In each arm, 31% of patients were poor risk for all three criteria. The median CD4+ cell count was 12.5 cells/mm^3 in the **CAELYX** arm and 13 cells/mm^3 in the ABV arm. The majority of patients had 25 or more lesions (74.6% in the **CAELYX** group and 69.7% in the ABV group).

Most patients in each arm were taking a variety of medication. In the **CAELYX** arm, 52.6% of patients were taking anti-retroviral drugs compared with 63.2% in the ABV arm. More than half the patients (56.4% **CAELYX** and 57.6% ABV) were taking acyclovir, 64.7% of **CAELYX** patients were taking co-trimoxazole compared with 64.0% of ABV patients and fluconazole was used in 72.2% of **CAELYX** patients and 71.2% of patients receiving ABV.

Overall there were significantly more responders in the patients randomised to **CAELYX**. The response rate for those receiving **CAELYX** was 46% compared with 26% for those receiving ABV ($p < 0.001$). The median time to CR or PR was 38 days for **CAELYX** and 50 days for ABV ($p = 0.014$)

where the time to response was recorded as the time the best response occurred relative to the time of beginning treatment. Once response occurred, the duration of response was very similar in each group, the median duration of response was 90 days for the **CAELYX** group compared with 92 days for ABV (p = 0.234). The response rate at the end of treatment was 36.1% for the **CAELYX** group and 21.5% for those receiving ABV (p = 0.023). Two-thirds of the patients randomised to **CAELYX** completed 6 cycles of treatment and one-third of those randomised to ABV completed the protocol. This corresponded to a total number of doses of 692 in the **CAELYX** group and 479 in the ABV group. Of those patients who discontinued early, adverse events were the cause of discontinuation for 14 patients in the **CAELYX** arm and 46 in the ABV arm.

With respect to the efficacy of **CAELYX** in patients who have failed prior chemotherapy, a retrospective analysis was conducted in refractory patients enrolled into one of the non- randomised studies. For the best conservative response (best response maintained for at least 3 weeks) in the 77 patients in this group, the response rate by the investigator assessment was 44%. The response was reached in a mean time of 128 days and continued for 118 days. In forty-nine of these patients who had received prior doxorubicin, the response rate by investigator assessment was 44.9%, and in 43 patients who had disease progression on prior doxorubicin the response rate was 39.5%.

5.2 Pharmacokinetic properties

CAELYX is a long-circulating pegylated liposomal formulation of doxorubicin HCl that provides greater concentration of doxorubicin in Kaposi's sarcoma (KS) tumours than in normal skin. 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 100nm) 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 HCl encapsulated during liposome residence time in circulation.

The plasma pharmacokinetics of **CAELYX** in humans differs significantly from those reported in the literature for standard doxorubicin HCl preparations. At lower doses (10mg/m^2 – 20mg/m^2) **CAELYX** displayed linear pharmacokinetics. Over the dose range of 10mg/m^2 – 60mg/m^2 **CAELYX** displayed non-linear pharmacokinetics. Standard doxorubicin HCl displays extensive tissue distribution (volume of distribution, 700 to 1100L/m^2) and a rapid elimination clearance (24 to 73L/h/m^2). In contrast, the pharmacokinetic profile of **CAELYX** indicates that **CAELYX** is confined mainly 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 HCl (containing 90% to 95% of the measured doxorubicin) are significantly higher than those achieved with standard doxorubicin HCl preparations.

Population pharmacokinetics

The pharmacokinetics of **CAELYX** were evaluated in 120 patients from 10 different clinical trials using the population pharmacokinetic approach. The pharmacokinetics of **CAELYX** over the dose range of 10mg/m^2 to 60mg/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 0.030L/h/m^2 (range 0.008 to 0.152L/h/m^2) and the mean volume of distribution at steady state was 2.43L/m^2 (range 1.10 – 4.85L/m^2). The apparent half-life ranged from 24 – 231 hours, with a mean of 73.9 hours.

There were no data for patients with severe renal or hepatic impairment.

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 0.016L/h/m^2 (range 0.009 - 0.027L/h/m^2), the mean central volume of distribution was 1.46L/m^2 (range 1.10 - 1.64L/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 0.021L/h/m^2 (range 0.009 – 0.041L/h/m^2), the mean volume of distribution at steady state was 1.95L/m^2 (range 1.67 – 2.40L/m^2). The mean apparent half-life was 75.0 hours (range 36.1 – 125 hours).

AIDS-KS patients
The plasma pharmacokinetics of **CAELYX** were evaluated in 23 patients with Kaposi's sarcoma who received single doses of 20mg/m^2 administered by a 30-minute infusion. The pharmacokinetic parameters of **CAELYX** (primarily representing liposome-encapsulated doxorubicin and low levels of unencapsulated doxorubicin HCl) observed after the 20mg/m^2 doses are presented in the following table.

Table 12: PHARMACOKINETIC PARAMETERS IN CAELYX-TREATED AIDS-KS PATIENTS	
	Mean ± Standard error
Parameter	20mg/m^2 n = 23
Maximum Plasma Concentration[a] (μg/mL.h)	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 ± 58.7
λ1 half-life (hours)	5.2 ± 1.4
λ2 half-life (hours)	55.0 ± 4.8
[a] Measured at the end of a 30-minutes infusion.	

In patients receiving 20mg/m^2 **CAELYX** the concentration of total (liposome encapsulated and unencapsulated) doxorubicin in the KS lesions was a median of 19 (range 3 - 53) times higher than in normal skin at 48 hours post-treatment.

The concentration of bioavailable (unencapsulated) doxorubicin in tissues is unknown because the assay procedure cannot distinguish between liposome encapsulated and unencapsulated doxorubicin.

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 prolonged infusions of doxorubicin HCl. With **CAELYX**, the encapsulation of doxorubicin in pegylated liposomes results in differing effects as follows:

Cardiotoxicity
Studies in rats, rabbits and dogs have shown that the cardiotoxicity of **CAELYX** is reduced compared to equivalent doses of unencapsulated doxorubicin HCl.

Dermal toxicity
In studies performed after the repeated administration of **CAELYX** to rats, rabbits 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 4.4: Palmar-plantar erythrodysesthesia).

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 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
A subcutaneous tolerance study in rabbits indicated that equivalent doses of **CAELYX** and unencapsulated doxorubicin HCl caused comparable local irritation. The resulting tissue damage was slightly less after subcutaneous **CAELYX** compared to unencapsulated doxorubicin HCl.

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 of **CAELYX** in patients has not suggested a significant nephrotoxicity liability of **CAELYX**, these findings in monkeys may not have relevance to patient risk assessment.

Carcinogenicity and mutagenicity
Although no studies have been conducted with **CAELYX**, doxorubicin HCl, the pharmacologically active ingredient of **CAELYX**, is mutagenic and carcinogenic. Pegylated placebo liposomes are neither mutagenic nor genotoxic at dose levels exceeding the maximum tolerated dose of **CAELYX**.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The concentration injection contains:
Ammonium sulfate
Sodium methoxy-PEG-40-carbonyl-distearoyl phosphatidylethanolamine (MPEG-DSPE)
(i.e. *Carbamoyl-methoxypolyethulene glycol distearoyl glycerophosphoethanolamine sodium*)
Hydrogenated soy phosphatidylcholine [HSPC] (i.e. *Lecithin*)
Cholesterol
Histidine
Sucrose
Water for Injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment).

Contains less than 1 mmol sodium (23mg) per dose, and is essentially ‘sodium-free’.

6.2 Incompatibilities

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

6.3 Shelf life

20 months. The expiry date can be found on the packaging.

Stability after reconstitution and dilution

After dilution with 5% Glucose Intravenous Infusion, the diluted **CAELYX** solution should be used immediately.

Diluted product not for immediate use should be prepared under aseptic conditions and in line with good pharmaceutical practice should be stored at 2°C to 8°C for no longer than 24 hours.

Partially used vials should be discarded.

6.4 Special precautions for storage

Store at 2°C to 8°C. Refrigerate. 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 10mL (20mg) or 25mL (50mg).

CAELYX 20mg/10mL concentrated injection is supplied in packs of one.

CAELYX 50mg/25mL concentrated injection is supplied in packs of one.

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 foreign particulate matter.
Do not mix with other drugs.

Determine the dose of **CAELYX** to be administered (based upon the recommended dose and the patient's surface area). Each **CAELYX** vial contains a deliverable volume of 10mL for the 20mg vial or 25mL for the 50mg vial (there is a small overage of suspension in the vial to account for losses during withdrawal). 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% Glucose Intravenous Infusion prior to administration. For doses < 90mg, dilute **CAELYX** in 250mL, and for doses > 90mg, dilute **CAELYX** in 500mL.

The use of any diluent other than 5% Glucose Intravenous 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% Glucose Intravenous Infusion 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.

Caution should be exercised in handling **CAELYX** suspension. The use of gloves is required. If **CAELYX** comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water.

CAELYX should be handled and disposed of in a manner consistent with that of other anti-cancer drugs.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

CAELYX *is distributed in New Zealand by:*

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
29 May 1997.

10 DATE OF REVISION OF THE TEXT

25 February 2026.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Additional information on renal and urinary disorders for patients with high cumulative exposure to pegylated liposomal doxorubicin.
4.9	Overdose contact details text updated.

Based on Australian PI most recent amendment 15 January 2026 [PI v4.0].

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.