Baxter

CAELYX® Concentrate for Infusion
Pegylated liposomal doxorubicin hydrochloride

International Non-Proprietary Name
Pegylated liposomal doxorubicin hydrochloride
FOR SINGLE USE INTRAVENOUS ADMINISTRATION

DOSAGE FORMS AND STRENGTHS
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.
Each CAELYX® vial contains 2 mg/ml doxorubicin hydrochloride in a pegylated liposomal formulation and delivers 10 ml (20 mg) or 25 ml (50 mg) in a concentrate for infusion for single intravenous use and is presented as a sterile, translucent, red suspension.
For excipients, see Section Pharmaceutical Particulars

PHARMACEUTICAL FORM
CAELYX® is a sterile, translucent, red liposomal dispersion, concentrate for intravenous infusion only.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances), ATC code: L01DB01.

The active ingredient of CAELYX® is doxorubicin hydrochloride, a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius*. CAELYX® is a long-circulating pegylated liposomal formulation of doxorubicin HCl that provides greater concentration of doxorubicin in Kaposi's sarcoma tumors than in normal skin. Pegylated liposomes contains 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 tumors. Evidence of penetration of pegylated liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C-26 colon carcinoma tumors 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.

Mechanism of action
The exact mechanism of the antitumor 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.

Pharmacodynamic effects
Clinical Efficacy
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: 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.

OVARIAN CANCER: 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.

MULTIPLE MYELOMA: A phase III randomized, 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 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.

Pharmacokinetic Properties
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.
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 – 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.

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 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 – 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 0.009 - 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-KS Patients: The plasma pharmacokinetics of CAELYX® were evaluated in 23 patients with Kaposi's (KS) sarcoma who received single doses of 20 mg/m^2 administered by a 30-minute infusion. The pharmacokinetic parameters of CAELYX® (primarily representing liposome-encapsulated doxorubicin HCl and low levels of unencapsulated doxorubicin HCl) observed after the 20 mg/m^2 doses are presented in Table 8.

Table 8: Pharmacokinetic Parameters in CAELYX® -Treated AIDS-KS Patients

	Mean ± Standard Error
Parameter	**20 mg/m² (n=23)**
Maximum Plasma Concentration* (µg/ml)	8.34 ± 0.49
Plasma Clearance (l/h/m²)	0.041 ± 0.004
Volume of Distribution (l/m²)	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

NON-CLINICAL INFORMATION

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 HCl 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 some patients after repeated administration (see **Adverse Reactions**).

Anaphylactoid response:
During repeat dose toxicology studies in dogs, an acute response characterized 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® or 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 compared with standard doxorubicin HCl, causes slighter local irritation or damage to the tissue after a possible extravasation.

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 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.

Reproductive toxicology:
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.

CLINICAL INFORMATION

Indications

CAELYX® is indicated:

- As monotheraphy for patients with metastatic breast cancer, where there is an increased cardiac risk. For patient who have received prior adjuvant anthracyclines (epirubicin or doxorubicin), Left Ventricular Ejection Fraction (LVEF) assessment should be performed before each additional administration of Caelyx that exceed a lifetime, doxorubicin-equivalent, cumulative anthracycline dose of 450 mg/m2.
- For the treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.
- For the treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (<200 CD 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 anthracyclines).
- Multiple Myeloma
  In combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy.

DOSAGE AND ADMINISTRATION:

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

Dosage

Breast/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/m^2 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/m^2 on days 1, 4, 8, and 11 every 3 weeks. The dose should be repeated as long as patients respond satisfactorily and tolerate treatment.

AIDS-KS patients:

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

Guidelines for CAELYX Dose Modification

To manage adverse events such as palmar-plantar erythrodysesthesia (PPE), stomatitis or hematologic 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 2) and stomatitis (Table 3) 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 hematologic toxicity (Table 4) 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 Adverse Reactions.

Guidelines For CAELYX® Dose Modification

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 hospitalization)	**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, edema, 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. HEMATOLOGICAL 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 8 and 9 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 < 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 Hemoglobim < 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 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 Prescribing Information for bortezomib

* for more information on bortezomib dosing and dosage adjustment, see the Prescribing Information for bortezomib.

Special Populations
Pediatric patients:
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®.

Renal impairment:
As doxorubicin is metabolized 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 30-156 ml/min) do not alter the pharmacokinetics of CAELYX®. No pharmacokinetic data are available in patients with creatinine clearance of less than 30 ml/min.

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.

Other populations
AIDS-KS patients with splenectomy: As there is no experience with CAELYX® in patients with splenectomy, treatment with CAELYX® is not recommended**.**

Administration
For doses < 90 mg: dilute CAELYX® in 250 ml Dextrose 5 % in Water.
For doses ≥ 90 mg: dilute CAELYX® in 500 ml Dextrose 5 % in Water.
If the patient experiences early symptoms or signs of infusion reaction, immediately discontinue the infusion, give appropriate premedications (antihistamine and/or short acting corticosteroid) and restart at a slower rate.
DO NOT administer as a bolus injection or undiluted dispersion. It is recommended that the CAELYX® infusion line be connected through the side port of an intravenous infusion of Dextrose 5% in Water to achieve further dilution and minimize the risk of thrombosis and extravasation. The infusion may given through a peripheral vein. CAELYX® must not be given by the intramuscular or subcutaneous route. Do not use with in-line filters.

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

In those patients who experience an infusion reaction, method of infusion should be modified 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.

Multiple myeloma
The intravenous catheter and tubing should be flushed with 5 % glucose solution for infusion between administration of the 2 medicinal products. 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:

- 10 ml over first 10 minutes
- 20 ml over next 10 minutes
- 40 ml 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:

- 10 ml over first 10 minutes
- 20 ml over next 10 minutes
- 40 ml 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-KS patients
CAELYX®, diluted in 250 ml Dextrose 5% in Water, is administered by intravenous infusion over 30 minutes.

ADVERSE REACTIONS
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of pegylated liposomal doxorubicin based on the comprehensive assessment of the available adverse event information. A causal relationship with pegylated liposomal doxorubicin cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data
Breast Cancer Patients: 254 patients with advanced breast cancer who had not received prior chemotherapy for metastatic disease were treated with CAELYX® at a dose of 50 mg/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). These effects were mostly mild and reversible, with 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. Infrequently, these effects resulted in permanent treatment discontinuation (7.0 % and 0 %, respectively). Pronounced or total alopecia was seen in only 7.0 % of CAELYX®-treated patients as compared with 54.0 % of patients treated with doxorubicin.
Hematologic adverse effects were infrequently reported and were mostly mild or moderate in severity and manageable. Anemia, neutropenia, leukopenia and thrombocytopenia were infrequently reported at incidences of 5.0 %, 4.0 %, 2.0 %, and 1.0 %, respectively. Life threatening (Grade IV) hematologic 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) (see **Dosage and Administration**).
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 hematologic measurements were infrequent as measured by leukopenia (4.3 %), anemia (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.
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 50 mg/m^2 every 4 weeks in a phase III clinical trial (C/I96-352), the safety profile was consistent with that reported for CAELYX® in previous studies using the same dosage regimen (see Table 5). 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 leukopenia (20 %).

Table 5: Treatment Related Undesirable Effects Reported in Breast Cancer Clinical Trials (I97-328 and C/I96-352) (≥ 5 % of CAELYX® -treated patients) by Severity, Body System and Preferred Term				
AE by body system	**I97-328 All Severities %**	**I97-328 Grades III/IV %**	**C/I96-352 All Severities %**	**C/I96-352 Grades III/IV %**
Autonomic Nervous System				
Flushing	3	< 1	5	< 1
Body as a whole				
Asthenia	10	1	9	1
Erythema	7	< 1	6	2
Fatigue	12	< 1	20	4
Fever	8	0	4	< 1
Weakness	6	< 1	0	0
Weight Decrease	3	< 1	5	0
Gastrointestinal system				
Abdominal Pain	8	1	4	< 1
Anorexia	11	1	11	0
Constipation	8	< 1	5	0
Diarrhea	7	1	10	< 1
Dyspepsia	3	0	5	0
Mouth Ulceration	5	< 1	< 1	0
Mucositis	23	4	14	3
Nausea	37	3	31	3
Stomatitis	22	5	21	5
Vomiting	19	< 1	19	4
Red Blood Cell Disorders				
Anemia	5	1	2	0
Respiratory System				
Dyspnea	2	1	6	3
Skin and Appendages				
Alopecia	20	0	3	0
Dry skin	2	0	5	0
PPE*	48	17	37	19
Pigmentation abnormal	8	< 1	< 1	0
Pruritus	3	< 1	5	0
Rash	10	2	15	2
Skin Discoloration	2	0	5	< 1

* 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.

Other Clinical Trial Data in Breast Cancer

Adverse reactions reported between 1 % and <5 % in 404 CAELYX®-treated breast cancer patients, not previously reported in CAELYX® clinical trials were breast pain, leg cramps, edema, leg edema, 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.

Ovarian Cancer Patients: 512 patients with ovarian cancer (a subset of 876 solid tumor patients) were treated with CAELYX® at a dose of 50 mg/m^2 every 4 weeks in clinical trials. The most frequently reported treatment related adverse effects included palmar-plantar erythrodysesthesia (PPE) (46.1 %) and stomatitis (38.9 %) (see Table 6). These effects were mainly mild, with severe (Grade III) cases reported in 19.5 % and 8.0 % respectively, and life threatening (Grade IV) cases reported in 0.6 % and 0.8 % respectively. These resulted infrequently in permanent treatment discontinuation (< 5 % and < 1 %, respectively).

Table 6: Treatment Related Undesirable Effects Reported In Ovarian Cancer Clinical Trials (≥ 5 % of CAELYX® -treated patients) By Severity (Grade III, IV), Body System And COSTART Preferred Term (N=512)			
AE by Body System	**Grade III %**	**Grade IV %**	**ALL %**
Body as a Whole			
Asthenia	7	-	34
Mucous Membrane Disorder	3	-	15
Fever	<1	-	9
Abdominal Pain	2	-	8
Pain	1	-	7
Digestive System			
Stomatitis	8	<1	39
Nausea	4	<1	38
Vomiting	4	<1	24
Constipation	<1	-	13
Anorexia	<1	-	12
Diarrhea	2	-	12
Dyspepsia	<1	-	6
Hemic and Lymphatic System			
Leukopenia	7	2	33
Anemia	6	<1	32
Neutropenia	9	3	32
Thrombocytopenia	1	<1	11
Nervous system			
Paresthesia	<1	-	8
Somnolence	<1	-	5
Respiratory System			
Pharyngitis	<1	-	6
Skin and Appendages			
Hand Foot Syndrome*	20	<1	46
Rash	3	<1	25
Alopecia	1	-	17
Skin Discoloration	-	-	6
Dry Skin	-	-	6

* PPE

Myelosuppression was mostly mild or moderate and manageable. Leukopenia was the most frequently reported hematologic adverse effect, followed by anemia, neutropenia and thrombocytopenia. Life threatening (Grade IV) hematologic effects were reported at incidences of 1.6 %, 0.4 %, 2.9 %, 0.2 %, respectively. Growth factor support was required infrequently (< 5 %) and transfusion support was required in approximately 15 % of patients (see Dosage and Administratrion).

Incidence 1-5%
Infections and infestations: Infection, oral moniliasis, herpes zoster, urinary tract infection
Blood and lymphatic system disorders: Hypochromic anaemia
Immune system disorders: Allergic reaction
Metabolism and Nutrition disorders: Dehydration, cachexia
Psychiatric disorders: Anxiety, depression, insomnia
Nervous system disorders: Headache, dizziness, neuropathy, hypertonia
Eye disorders: Conjunctivitis
Cardiac disorders: Cardiovascular disorder
Vascular disorders: Vasodilatation
Respiratory, thoracic and mediastinal disorders: Dyspnoea, increased cough
Gastrointestinal disorders: Mouth ulceration, esophagitis, nausea and vomiting, gastritis, dysphagia, dry mouth, flatulence, gingivitis, taste perversion
Skin and subcutaneous tissue disorders: Vesiculobullous rash, pruritus, exfoliative dermatitis, skin disorder, maculopapular rash, sweating, acne, skin ulcer

Musculoskeletal and connective tissue disorders: Back pain, myalgia
Renal and urinary disorders: Dysuria
Reproductive system and breast disorders: Vaginitis
General disorders and administration site conditions: Chills, chest pain, malaise, peripheral oedema
Investigations: Weight loss

In the 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 %). Clinically significant measurements, measured by Grades III and IV neutropenia (11.4 %), anemia (5.7 %), and thrombocytopenia (1.2 %) were low. Increases in AST were less frequently (< 1 %) reported. Sepsis related to leukopenia was observed infrequently (< 1 %).
Solid tumor patients: in a larger cohort of 929 patients with solid tumors (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 were comparable to those of the patients treated in the pivotal breast cancer and ovarian cancer trials.

Multiple Myeloma Patients: 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/m^2 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.

Treatment Related Undesirable Effects Reported in Multiple Myeloma MMY-3001 Clinical Trial (CAELYX® 30 mg/m² I.V. on day 4 in combination with bortezomib) (≥ 1 % of Caelyx-treated patients) by Severity, MedDRA System Organ Class and Preferred Term		
AE by Body System	**Multiple Myeloma All Severities n=318 (%)**	**Multiple Myeloma Grades III/IV n=318 (%)**
Infections and Infestations		
Herpes simplex	8	0
Herpes zoster	6	1
Nasopharyngitis	3	0
Oral candidiasis	1	0
Pneumonia	3	2
Upper respiratory tract infection	4	<1
Blood and Lymphatic System Disorders		
Anaemia	18	7
Febrile neutropenia	3	3
Leukopenia	8	5
Lymphopenia	2	<1
Neutropaenia	33	28
Thrombocytopaenia	29	22
Metabolism and Nutrition Disorders		
Anorexia	16	1
Decreased appetite	8	<1
Dehydration	3	<1
Hyperkalaemia	2	<1
Hypocalcaemia	1	<1
Hypokalaemia	3	2
Hypomagnesaemia	2	0
Hyponatraemia	1	<1
Psychiatric Disorders		
Anxiety	2	<1
Insomnia	5	0
Nervous System Disorders		
Dizziness	6	1
Dysaesthesia	1	0
Dysgeusia	5	0
Headache	10	<1
Hypoaesthesia	2	0
Lethargy	3	<1
Neuralgia	14	3
Neuropathy	8	1
Paraesthesia	9	<1
Peripheral neuropathy	9	2
Peripheral sensory neuropathy	10	<1
Polyneuropathy	6	0
Syncope	1	<1
Eye Disorders		
Conjunctivitis	3	0
Vascular Disorders		
Flushing	2	0
Hypertension	1	<1
Hypotension	4	1
Orthostatic hypotension	3	<1
Phlebitis	1	0

Respiratory, Thoracic, and Mediastinal Disorders	3	0
Cough	5	<1
Dyspnoea	2	<1
Epistaxis	2	<1
Exertional dyspnoea		
Gastrointestinal Disorders		
Abdominal pain	7	<1
Aphthous stomatitis	1	0
Constipation	22	<1
Diarrhoea	35	7
Dry mouth	2	0
Dyspepsia	5	<1
Dysphagia	2	<1
Mouth ulceration	1	0
Nausea	40	2
Stomatitis	16	2
Upper abdominal pain	4	<1
Vomiting	28	4
Skin and Subcutaneous Tissue Disorders		
Allergic dermatitis	1	0
Alopecia	2	0
Drug Eruption	2	0
Dry skin	5	0
Erythema	3	0
Papular rash	3	0
Petechiae	2	0
PPE*	16	5
Pruritus	3	<1
Rash	11	<1
Skin hyperpigmentation	3	0
Musculoskeletal and Connective Tissue Disorders	4	<1
Arthralgia	2	0
Muscle spasms	2	0
Muscular weakness	1	0
Musculoskeletal chest pain	1	0
Musculoskeletal pain	3	0
Myalgia	5	0
Pain in extremity		
Reproductive system and breast disorders		
Scrotal erythema	1	<1
General Disorders and Administration Site Conditions	16	5
Asthenia	4	0
Chills	27	5
Fatigue	2	<1
Hyperthermia	3	<1
Influenza like illness	3	0
Malaise	4	0
Peripheral oedema	18	<1
Pyrexia		
Investigations		
Alanine aminotransferase increased	1	0
Aspartate aminotransferase increased	3	0
Blood creatinine increased	2	0
Ejection fraction decreased	3	0
Weight decreased	8	0

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

AIDS-KS Patients: Open-label and controlled clinical studies on AIDS-KS patients treated with CAELYX® at a dose of 20 mg/m^2 every 2 to 3 weeks show that myelosuppression was the most frequent side effect considered related to CAELYX®, occurring in approximately one-half of the patients. Leukopenia is the most frequent undesirable effect experienced with CAELYX® in this population; neutropenia, anemia and thrombocytopenia have been observed. These effects may occur early on in treatment. Hematological 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 hematological toxicity for breast cancer or ovarian cancer patients is less severe than in the AIDS-KS setting (see section for **Ovarian Cancer Patients** above).
Other frequently (≥ 5%) observed side effects were nausea, asthenia, alopecia, fever, diarrhea, infusion-associated acute reactions, and stomatitis.
Respiratory side effects frequently (≥ 5%) occurred in clinical studies of CAELYX® and may be related to opportunistic infections in the AIDS population. Opportunistic infections (OIs) are observed in AIDS-KS patients after administration with CAELYX®, and are frequently observed in patients with HIV-induced immunodeficiency. The most frequently observed OIs in clinical studies were candidiasis, cytomegalovirus, herpes simplex, *Pneumocystis carinii* pneumonia, and mycobacterium avium complex.

Other less frequently (< 5%) observed side effects included palmar-plantar erythrodysesthesia, oral moniliasis, nausea and vomiting, vomiting, weight loss, rash, mouth ulceration, dyspnea, abdominal pain, hypersensitivity reaction including anaphylactic reactions, vasodilatation, dizziness, anorexia, glossitis, constipation, paresthesia, retinitis, and confusion.
Clinically significant laboratory abnormalities frequently (≥ 5%) occurred in clinical studies with CAELYX®. These included increases in alkaline phosphatase and increases in AST and bilirubin which are believed to be related to the underlying disease and not CAELYX®. Reduction in hemoglobin and platelets were less frequently (< 5%) reported. Sepsis related to leukopenia 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 tumors 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 edema, hypotension, vasodilatation, urticaria, back pain, chest pain, chills, fever, hypertension, tachycardia, dyspepsia, nausea, dizziness, dyspnea, pharyngitis, rash, pruritus, sweating, injection site reaction and drug interaction. Permanent treatment discontinuation rates were infrequently reported at 2 %. A similar incidence of infusion reactions (12.4 %) was observed in the pivotal breast cancer trials. The rate of permanent treatment discontinuation was also similar at 1.5 %. 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 characterized by flushing, shortness of breath, facial edema, 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, these 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®.
Myelosuppression associated with anemia, thrombocytopenia, leukopenia, and rarely febrile neutropenia, has been reported in CAELYX®-treated patients. Stomatitis has been reported in patients receiving continuous infusions of conventional doxorubicin HCl 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.
Palmar-plantar erythrodysesthesia is characterized by painful, macular reddening 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 50-150 mg 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, 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 by 1-2 weeks or reducing the CAELYX® dose. This reaction can be severe and debilitating in some patients, however, and may require discontinuation of treatment.

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 tumor patients with cumulative anthracycline doses of 509 mg/m^2 – 1680 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 breast cancer trial comparing CAELYX® (50 mg/m^2 every 4 weeks) to doxorubicin (60 mg/m^2 every 3 weeks), 10/254 patients randomized to receive CAELYX® versus 48/255 patients randomized to receive doxorubicin met the protocol-defined criteria for cardiac toxicity during treatment and/or follow-up. Cardiac toxicity was defined as a decrease of 20 percentage points or greater from baseline if the resting LVEF remained in the normal range or a decrease of 10 percentage points or greater if the LVEF became abnormal (less than the lower limit for normal). The risk of developing a cardiac event as a function of cumulative anthracycline dose was significantly lower with CAELYX® than with doxorubicin (HR [doxorubicin/ CAELYX®] = 3.16, p<0.001).
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 tumors, 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 1532 mg/m^2, the incidence of clinically significant cardiac dysfunction was low. Of the 929 patients treated with CAELYX® 50 mg/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 > 400 mg/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 percentage points from baseline. Furthermore, only 1 patient (who received a cumulative dose of 944 mg/m^2), discontinued study treatment because of clinical symptoms of congestive heart failure.
Although local necrosis following extravasation has been reported very rarely, CAELYX® should be considered an irritant. Animal studies indicate that administration of doxorubicin HCl as a liposomal formulation reduces the potential for extravasation injury. 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.
Recall of skin reaction due to prior radiotherapy has rarely occurred with CAELYX® administration.

Postmarketing Data
Adverse drug reactions identified during the postmarketing experience with are described below. 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

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.

Skin and subcutaneous tissue disorders
Serious skin conditions including erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, and lichenoid keratosis have been reported very rarely.

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 (see **Warnings and Precautions**).

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. Therefore, any patient treated with doxorubicin should be kept under haematological supervision.

Overdose
Symptoms and signs
Acute overdosage with doxorubicin HCl worsens the toxic effects of mucositis, leukopenia and thrombocytopenia.

Treatment
Treatment of acute overdosage of the severely myelosuppressed patient consists of hospitalization, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

CONTRAINDICATIONS
CAELYX® is contraindicated in patients who have hypersensitivity reactions to its components or to doxorubicin HCl. CAELYX® should not be administered while breast-feeding.
CAELYX® should not be used to treat AIDS-KS that may be effectively treated with local therapy or systemic alfa-interferon.

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

Combination chemotherapy with CAELYX® has been extensively studied in solid tumor 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.

Cardiac risk:
All patients receiving CAELYX® should routinely undergo frequent electrocardiogram (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 (see **Adverse Reactions**).
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 should be applied routinely before the initiation of CAELYX® therapy and should be repeated periodically during treatment.
In a phase III clinical trial comparing CAELYX® (50 mg/m2 /every 4 weeks) versus doxorubicin (60 mg/m2/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 [doxorubicin/CAELYX®]=3.16, p<0.001). At cumulative doses between 450 mg/m2 and 600 mg/m2 there was no increased risk of cardiac toxicity with CAELYX®. 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 600 mg/m2 in patients without prior anthracycline exposure. For patients who have received prior adjuvant anthracyclines (epirubicin or doxorubicin), LVEF assessments should be performed before each additional administration of CAELYX® that exceeds a lifetime, doxorubicin-equivalent, cumulative anthracycline dose of 450 mg/m2.
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 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 **Adverse Reactions**).

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 tumors 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 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 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. 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, although not seen in patients with breast or ovarian cancer, may result in superinfection or hemorrhage.

Diabetic patients:
It should be noted that each vial of CAELYX® contains sucrose and is administered in dextrose 5% in water for intravenous infusion. (In the EU, 5% glucose solution for infusion is used.)

Infusion-associated reactions:
Serious and sometimes life-threatening infusion reactions, which are characterized by allergic-like or anaphylactoid-like reactions, with symptoms including asthma, flushing, urticarial rash, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial edema, chills, back pain, tightness in the chest and throat and/or hypotension may occur within minutes of starting the infusion of CAELYX®. Very rarely, convulsions have been observed in relation to infusion reactions. Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medications to treat these symptoms (e.g., antihistamines, corticosteroids, and adrenaline), 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 minimize the risk of infusion reactions, the initial dose should be administered at a rate no greater than 1 mg/minute (see **Adverse Reactions**).
For common adverse events which required dose modification or discontinuation in Multiple Myeloma patients see **Adverse Reactions**.

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.

INTERACTIONS

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 gynecological malignancies. Caution should be exercised in the concomitant use of drugs known to interact with standard doxorubicin HCl. CAELYX®, like other doxorubicin HCl preparations, may potentiate the toxicity of other anti-cancer therapies.

CAELYX® has been given as part of a combination therapy regimen (combined with either cyclophosphamide, taxanes or vinorelbine) to 230 patients with solid tumors (including ovarian cancer or breast cancer). The doses of CAELYX® and the combination agent used in these studies were as follows: cyclophosphamide 600 mg/m² + CAELYX® 30 mg/m² every 3 weeks, paclitaxel 175 mg/m² + CAELYX® 30 mg/m² every 3 weeks, docetaxel 60 mg/m² + CAELYX® 30 mg/m² every 3 weeks, and vinorelbine 30 mg/m² every 2 weeks + CAELYX® 40 mg/m² every 4 weeks. No new additive toxicities were noted. In patients with AIDS-KS, exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with standard doxorubicin HCl. Caution should be exercised when giving any other cytotoxic agents, especially myelotoxic agents, at the same time.

Pregnancy and Breast-feeding

Pregnancy

CAELYX® is embryotoxic in rats and embryotoxic and abortifacient in rabbits. Teratogenicity cannot be ruled out. There is no experience in pregnant women with CAELYX®. Therefore administration to pregnant woman is not recommended. Women of child-bearing potential should be advised to avoid pregnancy while they or their male partner are receiving CAELYX® and in the six months following discontinuation of CAELYX® therapy.

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.

Effects on Ability to Drive and Use Machines

Although CAELYX® should not affect driving performance, in clinical 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.

Pharmaceutical Particulars

List of Excipients

The following excipients are contained in each vial of product:

α-(2-[1,2-distearoyl-*sn*-glycero(3)phosphooxy]ethylcarbamoyl)-ω-methoxypoly (oxy ethylen)-40 sodium salt (MPEG-DSPE) [also known as N-(carbamoyl-methoxypolyethyleneglycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE)]; Fully Hydrogenated Soy Phosphatidylcholine (HSPC); Cholesterol, NF; Ammonium Sulphate; Sucrose, Ph Eur; Histidine, Ph. Eur.; Water for Injection, Ph. Eur.; Hydrochloric Acid, Ph. Eur.; Sodium Hydroxide, Ph. Eur.

Incompatibilities

DO NOT MIX WITH OTHER DRUGS

Shelf Life

20 months

After dilution:

- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.
- Partially used vials must be discarded.

Storage Conditions
Store in a refrigerator (2°C - 8°C).
Do not freeze.
For storage conditions of the diluted medicinal product, see **Shelf Life**
Keep out of the sight and reach of children.

Nature and Contents of Container
Type I glass vials, each with a siliconised grey bromobutyl stopper, and an aluminum 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.

Instructions for Use and Handling and Disposal
DO NOT USE MATERIAL THAT SHOWS EVIDENCE OF PRECIPITATION OR ANY OTHER PARTICULATE MATTER.
Caution should be exercised in handling CAELYX® dispersion. 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 anticancer drugs.
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 Dextrose 5% in Water prior to administration. For doses <90 mg, dilute CAELYX® in 250 ml, and for doses ≥ 90 mg, dilute CAELYX® in 500 ml of Dextrose 5 % in Water.
The use of any diluent other than Dextrose 5% in Water 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 Dextrose 5% in Water. The infusion may be given through a peripheral vein. **Do not use with in-line filters.**

HOW SUPPLIED
CAELYX Concentrate for Infusion
Box of 1 vial of 10 ml
Reg. No.: DKI1255202649A1

HARUS DENGAN RESEP DOKTER

Manufactured by GlaxoSmithKline Manufacturing S.P.A., Parma, Italy
Packaged and released by Janssen Pharmaceutica N.V., Beerse, Belgium
Imported and distributed by PT Soho Industri Pharmasi
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