

CAELYX Concentrate for Infusion

Brand of pegylated liposomal doxorubicin hydrochloride

FOR SINGLE USE INTRAVENOUS ADMINISTRATION

DESCRIPTION: 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 2mg/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. The active ingredient of CAELYX is doxorubicin HCl, a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius*.

Inactive ingredients: The following excipients are contained in each vial of product:

- α -(2-[1,2-distearoyl-*sn*-glycero(3)phospho]oxyethyl)carbamoyl- ω -methoxypoly(oxyethylene)-40 sodium salt (MPEG-DSPE)
- Fully Hydrogenated Soy Phosphatidylcholine (HSPC)
- Cholesterol, NF
- Ammonium Sulphate, ACS
- Sucrose, Ph Eur
- Histidine, Ph Eur
- Water for Injection, Ph Eur
- Hydrochloric Acid, Ph Eur
- Sodium Hydroxide, Ph Eur

ACTIONS: 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.

PRECLINICAL TOXICOLOGY: 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 patients after long-term intravenous infusion (see ADVERSE EFFECTS).

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 against standard doxorubicin HCl, causes slighter local irritation or damage to the tissue after a possible extravasation.

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

Reproductive toxicity: CAELYX resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 mg/kg. Decreased testicular weights and hypospermia were present in rats after repeat doses \geq 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.

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

CLINICAL PHARMACOLOGY: 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.

The plasma pharmacokinetics of CAELYX in humans differ significantly from those reported in the literature for standard doxorubicin hydrochloride preparations. At lower doses ($10 \text{ mg/m}^2 - 20 \text{ mg/m}^2$) CAELYX displayed linear pharmacokinetics. Over the dose range of $10 \text{ mg/m}^2 - 60 \text{ mg/m}^2$ CAELYX displayed non-linear pharmacokinetics. Standard doxorubicin hydrochloride displays extensive tissue distribution (volume of distribution, 700 to $1,100 \text{ l/m}^2$ and a rapid elimination clearance ($24 - 73 \text{ l/h/m}^2$). In contrast, the pharmacokinetic profile of CAELYX indicates that CAELYX is confined mostly to the vascular fluid volume and that the clearance of doxorubicin from the blood is dependent upon the liposomal carrier. Doxorubicin becomes available after the liposomes are extravasated and enter the tissue compartment.

At equivalent doses, the plasma concentration and AUC values of CAELYX which represent mostly pegylated liposomal doxorubicin hydrochloride (containing 90 % to 95 % of the measured doxorubicin) are significantly higher than those achieved with standard doxorubicin hydrochloride preparations.

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 $0.008 - 0.152 \text{ l/h/m}^2$) and the mean central volume of distribution was 1.93 l/m^2 (range $0.96 - 3.85 \text{ l/m}^2$) 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 $0.009 - 0.027 \text{ l/h/m}^2$), the mean central volume of distribution was 1.46 l/m^2 (range $1.10 - 1.64 \text{ l/m}^2$). 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/m² (range 0.009 – 0.041 l/h/m²), the mean central volume of distribution was 1.95 l/m² (range 1.67 – 2.40 l/m²). 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/m² 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/m² doses are presented in Table 1.

Table 1. Pharmacokinetic Parameters in CAELYX-Treated AIDS-KS Patients

Parameter	Mean ± Standard Error
	20 mg/m ² (n=23)
Maximum Plasma Concentration* (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)	590.00 ± 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

CLINICAL EFFICACY: 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.

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). PFS was similar for CAELYX and the active comparator, with a strong trend favoring CAELYX (HR=1.26, 95 % CI 0.98 - 1.62, p=0.11). In all subgroups analyzed, including those patients ≥ 55 years of age (n=166), there was a consistent treatment effect with PFS favoring CAELYX over the active comparator (all hazard ratios were > 1.00).

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.

INDICATIONS AND USAGE: CAELYX is indicated for

- Metastatic Breast Cancer in patients where there is an increased cardiac risk

CAELYX is indicated for the treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.

CAELYX is also indicated for AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (<200 CD4 lymphocytes/mm³) 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).

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.

Breast/Ovarian Cancer: CAELYX is administered intravenously at a dose of 50 mg/m² once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment.

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.

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 the breast cancer trial program, modification of the infusion was permitted for those patients experiencing an infusion reaction as follows:

5 % of the total dose was infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate was doubled for the next 15 minutes. If tolerated, the infusion was completed over the next hour for a total infusion time of 90 minutes.

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

AIDS-KS patients: CAELYX should be administered intravenously at 20 mg/m² 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 250 ml Dextrose 5% in Water, is administered by intravenous infusion over 30 minutes.

All patients: 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 solution. 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 be given through a peripheral vein. CAELYX must not be given by the intramuscular or subcutaneous route. Do not use with in-line filters.

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 EFFECTS.

Guidelines For CAELYX Dose Modification

Table 2. 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 3. 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)	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 4. 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 \geq 1,500 and platelets \geq 75,000; redose with no dose reduction.
Grade 3	500 – <1,000	25,000 - <50,000	Wait until ANC \geq 1,500 and platelets \geq 75,000; redose with no dose reduction.
Grade 4	<500	<25,000	Wait until ANC \geq 1,500 and platelets \geq 75,000; decrease dose by 25% or continue full dose with growth factor support.

Patients with impaired hepatic function: 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.

Patients with impaired renal function: 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.

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

Pediatric patients: Limited Phase I safety data indicate that doses up to 60 mg/m² every 4 weeks are well tolerated in pediatric patients; however, effectiveness in patients under 18 years of age has 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.

Instructions for use/handling

DO NOT USE MATERIAL THAT SHOWS EVIDENCE OF PRECIPITATION OR ANY OTHER PARTICULATE MATTER.

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

INCOMPATIBILITIES: DO NOT MIX WITH OTHER DRUGS

DRUG 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.

ADVERSE EFFECTS: 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/m² 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 or nausea. Infrequently, 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.

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/m² 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 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 Nose	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				
Pruritus	8	< 1	< 1	0
Rash	3	< 1	5	0
Skin Discoloration	10	2	15	2
	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.

Undesirable 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, 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/m² 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).

Undesirable Effect by Body System	Grade III %	Grade IV %	Total %
Body as a whole			
Asthenia	6.6	-	34.0
Mucous Membrane Disorder	3.1	-	14.5
Fever	0.4	-	9.4
Abdominal Pain	1.8	-	8.2
Pain	1.0	-	7.4
Digestive system			
Stomatitis	8.0	0.8	38.9
Nausea	4.1	0.2	38.1
Vomiting	4.3	0.6	24.4
Constipation	0.4	-	12.9
Anorexia	0.6	-	12.1
Diarrhea	1.6	-	11.7
Dyspepsia	0.4	-	5.5
Hemic and lymphatic system			
Leukopenia	7.0	1.6	33.2
Anemia	5.5	0.4	32.2
Neutropenia	9.0	2.9	31.6
Thrombocytopenia	1.2	0.2	10.7
Nervous system			
Paresthesia	0.2	-	7.6
Somnolence	0.4	-	5.1
Respiratory System			
Pharyngitis	0.6	-	6.4

Skin and appendages			
Hand Foot Syndrome*	19.5	0.6	46.1
Rash	3.3	0.2	25.0
Alopecia	1.2	-	17.4
Skin Discoloration	-	-	6.1
Dry Skin	-	-	5.9

*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 ADMINISTRATION).

Other less frequently (1 to 5 %) reported undesirable effects included peripheral edema, oral moniliasis, vasodilatation, mouth ulceration, pruritus, allergic reaction, dehydration, dyspnea, vesiculobullous rash, chills, infection, weight loss, esophagitis, skin disorder, exfoliative dermatitis, cardiovascular disorder, chest pain, dizziness, maculopapular rash, gastritis, myalgia, back pain, depression, insomnia, dysphagia, increased cough, sweating, nausea and vomiting, malaise, taste perversion, urinary tract infection, conjunctivitis, acne, gingivitis, herpes zoster, hypochromic anemia, anxiety, vaginitis, headache, flatulence, dry mouth, cachexia, neuropathy, hypertonia, skin ulcer and dysuria.

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/m² every 4 weeks, the safety profile and incidence of adverse effects are comparable to those of the patients treated in the pivotal breast cancer and ovarian cancer trials.

AIDS-KS patients: Open-label and controlled clinical studies on AIDS-KS patients treated with CAELYX at a dose of 20 mg/m² 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 $< 1,000 /\text{mm}^3$ and/or the platelet count is $< 50,000 /\text{mm}^3$. G-CSF (or GM-CSF) may be given as concomitant therapy to support the blood count when the ANC count is $< 1,000 /\text{mm}^3$ 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 ($\geq 5\%$) observed side effects were nausea, asthenia, alopecia, fever, diarrhea, infusion-associated acute reactions, and stomatitis.

Respiratory side effects frequently ($\geq 5\%$) 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 ($\geq 5\%$) 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 AIDS-KS, infusion-associated reactions, were characterised 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, infusion-associated reactions occurred primarily during the first infusion. Temporarily stopping the infusion usually resolves these symptoms without further therapy. In nearly all patients, CAELYX treatment can be resumed after all symptoms have resolved without recurrence. Infusion reactions rarely recur after the first treatment cycle with CAELYX.

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, which may be initiated 4 to 7 days after treatment with CAELYX includes 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 dose interval 1-2 weeks or reducing the 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 $> 450\text{mg}/\text{m}^2$ 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 $460\text{mg}/\text{m}^2$ indicate no evidence of anthracycline-induced cardiomyopathy. The recommended dose of CAELYX for AIDS-KS patients is $20\text{mg}/\text{m}^2$ every two-to-three weeks. The cumulative dose at which cardiotoxicity would become a concern for these AIDS-KS patients ($> 400\text{mg}/\text{m}^2$) 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 $509\text{mg}/\text{m}^2$ – $1680\text{mg}/\text{m}^2$. 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 50 mg/m²/every 4 weeks) versus 48/255 patients randomized to receive doxorubicin (treated at a dose of 60 mg/m²/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 tumors, including a subset of patients with breast and ovarian cancers, treated at a dose of 50 mg/m²/cycle with lifetime cumulative anthracycline doses up to 1532 mg/m², the incidence of clinically significant cardiac dysfunction was low. Of the 929 patients treated with CAELYX 50 mg/m²/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/m², 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 944 mg/m²), 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.

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

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.

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.

PRECAUTIONS: 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 EFFECTS).

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=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 which exceeds a lifetime cumulative anthracycline dose of 600mg/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/m² 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/m²) is similar to the 20 mg/m² profile in patients with AIDS-KS (see ADVERSE EFFECTS).

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/m², 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.

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.

Diabetic patients: It should be noted that each vial of CAELYX contains sucrose and is administered in Dextrose 5% in Water for Intravenous Infusion.

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 also have been observed in relation to infusion reactions** (see ADVERSE EFFECTS). 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 minimize the risk of infusion reactions, the initial dose should be administered at a rate no greater than 1 mg/minute (see DOSAGE AND ADMINISTRATION).

Effect 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.

USAGE DURING PREGNANCY AND LACTATION: 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.

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.

OVERDOSAGE INFORMATION: 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 hospitalization, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

HOW SUPPLIED: Caelyx (doxorubicin hydrochloride, pegylated liposomal) concentrate for infusion is contained in 10 ml clear glass vial. Each vial contains doxorubicin hydrochloride pegylated liposomal 20 mg.

STORAGE: Unopened vials of material should be stored at 2°C to 8°C. Avoid freezing. After dilution with Dextrose 5% in Water for Intravenous Infusion, the diluted CAELYX solution should be used immediately. Diluted product not for immediate use should be stored at 2°C to 8°C for no longer than 24 hours. Partially used vials should be discarded.

Manufactured by
Ben Venue Laboratories Inc.
Bedford, Ohio 44146
USA



[Imported and](#) Marketed in India by
Fulford (I) Limited
Eureka Towers, 8th Floor,
Mind Space, Link Road,
Malad (W), Mumbai 400 064

For the use of a Registered
Medical Practitioner /
Hospital only

* Trademark

© 1996, 1997, 1999, 2000, 2002, 2004, 2006 Schering-Plough Pharmaceuticals

Kenilworth, New Jersey, U.S.A.

ALL RIGHTS RESERVED

Deleted: ¶