SG - 745503

CAELYX®

PRODUCT NAME
CAELYX® Concentrate for Infusion
(pegylated liposomal doxorubicin hydrochloride)

FOR SINGLE USE INTRAVENOUS ADMINISTRATION

DOSAGE FORMS AND STRENGTHS
CAELYX® is a sterile, translucent, red liposomal dispersion, concentrate for intravenous infusion only.

Each CAELYX® vial contains 2 mg/mL doxorubicin HCl 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.

For excipients, see "*List of Excipients*".

CLINICAL INFORMATION
Indications
Breast Cancer
CAELYX®, as monotherapy, is indicated for the treatment of metastatic breast cancer.

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

Multiple Myeloma
CAELYX® is indicated in combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and have not previously received bortezomib. Patients should have already undergone or are unsuitable for bone marrow transplant.

AIDS-related Kaposi's Sarcoma
CAELYX® is also indicated for AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (<200 CD4 lymphocytes/mm^3) and extensive mucocutaneous or visceral disease.

CAELYX® may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other 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/m^2 once every four 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 20mg/m^2 every two-to-three weeks. Intervals shorter than 10 days should be avoided as drug accumulation and increased toxicity cannot be ruled out. Patients should be treated for two-to-three months to achieve a therapeutic response. Treatment should be continued as needed to maintain a therapeutic response.

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 1) and stomatitis (Table 2) provide the schedule followed for dose modification in clinical trials in the treatment of breast or ovarian cancer (modification of the recommended 4 week treatment cycle): If these toxicities occur in patients with AIDS-related KS, the recommended 2 to 3 week treatment cycle can be modified in a similar manner.

The table for hematologic toxicity (Table 3) provides the schedule followed for dose modification in clinical trials in the treatment of patients with breast or ovarian cancer only. Dose modification in patients with AIDS-KS is addressed in *Adverse Reactions*.

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**	**Discontinue CAELYX®**
Grade 4 (diffuse or local process causing infectious complications, or a bedridden state or hospitalization)	**Wait an additional week**	**Wait an additional week**	**Discontinue CAELYX®**

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**	**Discontinue CAELYX®**
Grade 4 (requires parenteral or enteral support)	**Wait an additional week**	**Wait an additional week**	**Discontinue CAELYX®**

Table 3. HEMATOLOGICAL TOXICITY (ANC OR PLATELETS) – MANAGEMENT OF PATIENTS WITH BREAST OR OVARIAN CANCER

GRADE	ANC	PLATELETS	MODIFICATION
Grade 1	1500 – 1900	75000 - 150000	Resume treatment with no dose reduction.
Grade 2	1000 - <1500	50000 - <75000	Wait until ANC ≥1500 and platelets ≥75000; redose with no dose reduction.
Grade 3	500 – <1000	25000 - <50000	Wait until ANC ≥1500 and platelets ≥75000; redose with no dose reduction.
Grade 4	<500	<25000	Wait until ANC ≥1500 and platelets ≥75000; decrease dose by 25% or continue full dose with growth factor support.

For multiple myeloma patients treated with CAELYX® in combination with bortezomib who experience PPE or stomatitis, the CAELYX® dose should be modified as described in Table 1 and 2 above respectively. 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 Hemoglobin < 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

Pediatric patients
Limited Phase I safety data indicate that doses up to 60 mg/m^2 every 4 weeks are well tolerated in pediatric patients; however, effectiveness in patients less than 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®.

Patients with impaired renal function
As doxorubicin is metabolised by the liver and excreted in the bile, dose modification should not be required with CAELYX®. Population-based analysis confirms that changes in renal function over the range tested (estimated creatinine clearance 30-156 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.

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 × 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.

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 be 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 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.

Multiple myeloma
The intravenous catheter and tubing should be flushed with 5% glucose solution for infusion between administration of CAELYX® and bortezomib. Day 4 dosing of both medicinal products may be delayed up to 48 hours as medically necessary. Doses of bortezomib should be at least 72 hours apart. The first infusion of CAELYX® should be administered over 90 minutes, as follows:
1. 10 mL over first 10 minutes
2. 20 mL over next 10 minutes
3. 40 mL over next 10 minutes
4. 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:
5. 10 mL over first 10 minutes
6. 20 mL over next 10 minutes
7. 40 mL over next 10 minutes
8. 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.

Contraindications
CAELYX® is contraindicated in patients who have hypersensitivity reactions to its components or to doxorubicin HCl. CAELYX® should not be administered during pregnancy or while breast-feeding.

CAELYX® should not be used to treat AIDS-KS that may be effectively treated with local therapy or systemic alfa-interferon.

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/m^2 /every 4 weeks) versus doxorubicin (60 mg/m^2/every 3 weeks), the risk of developing a cardiac event as a function of cumulative anthracycline dose was significantly lower with CAELYX® than with doxorubicin (HR=3.16, p<0.001). At cumulative doses between 450 mg/m^2 and 600 mg/m^2 there was no increased risk of cardiac toxicity with CAELYX®. The evaluation of left ventricular function is considered to be mandatory before each additional administration of CAELYX® which exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2.

The evaluation tests and methods mentioned above concerning the monitoring of cardiac performance during anthracycline therapy 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 anthracyclines 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.

In controlled clinical studies in patients with AIDS-KS against a bleomycin/vincristine regimen, opportunistic infections were apparently more frequent during treatment with CAELYX®. Patients and doctors must be aware of this higher incidence and take action as appropriate.

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 Reactions*). Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medications to treat these symptoms (e.g., antihistamines, corticosteroids, adrenaline and anticonvulsants), as well as emergency equipment should be available for immediate use. In most patients treatment can be resumed after all symptoms have resolved, without recurrence. Infusion reactions rarely recur after the first treatment cycle. To 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*).

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/m^2 + CAELYX® 30 mg/m^2 every 3 weeks, paclitaxel 175 mg/m^2 + CAELYX® 30 mg/m^2 every 3 weeks, docetaxel 60 mg/m^2 + CAELYX® 30 mg/m^2 every 3 weeks, and vinorelbine 30 mg/m^2 every 2 weeks + CAELYX® 40 mg/m^2 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 women 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.

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.

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. 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
509 patients with advanced breast cancer who had not received prior chemotherapy for metastatic disease were treated with CAELYX® (n=254) at a dose of 50 mg/m^2 every 4 weeks or doxorubicin (n=255) at a dose of 60 mg/m^2 every 3 weeks in a phase III clinical trial (I97-328). The 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).

Mucositis (23% vs 13%; Grade III/IV 4% vs 2%), and stomatitis (22% vs 15%; Grade III/IV 5% vs 2%) were reported more commonly with CAELYX® than with doxorubicin. The following common adverse events were reported more often with doxorubicin than with CAELYX®: nausea (53% vs 37%; Grade III/IV 5% vs 3%), vomiting (31% vs 19%; Grade III/IV 4% vs less than 1%) and neutropenia (10% vs 4%; Grade III/IV 8% vs 2%). 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. The average duration of the most common severe (Grade III/IV) events for both groups was 30 days or less.

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 Adverse Reactions Reported in Breast Cancer Clinical Trials (I97-328 and I96-352) (≥ 5 % of CAELYX®-treated patients) by Severity, Body System and Preferred Term

Adverse Reaction 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 (≥ 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/m^2 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 Adverse Reactions Reported in Ovarian Cancer Clinical Trials (≥ 5 % of CAELYX®-treated patients) by Severity (Grade III, IV), Body System and COSTART Preferred Term (n=512)

Adverse Reaction 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

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*).

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: Dyspnea, 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 edema

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 are 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 8 for adverse effects reported in ≥ 5% patients treated with combination therapy of CAELYX® plus bortezomib.

Neutropenia, thrombocytopenia, and anemia 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 neutropenia was higher in the combination therapy group than in the monotherapy group (28% vs. 14%).The incidence of grade 3 and 4 thrombocytopenia was higher in the combination therapy group than in the monotherapy group (22% vs. 14%). The incidence of anemia 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, thrombocytopenia, decreased ejection fraction, and fatigue.

Table 7. Treatment Related Adverse Reactions Reported in Multiple Myeloma MMY-3001 Clinical Trial (CAELYX® 30 mg/m^2 I.V. on day 4 in combination with bortezomib) (≥ 1 % of CAELYX®-treated patients) by Severity, MedDRA System Organ Class and Preferred Term

Adverse Reaction 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		
Anemia	18	7
Febrile neutropenia	3	3
Leukopenia	8	5
Lymphopenia	2	<1
Neutropenia	33	28
Thrombocytopenia	29	22
Metabolism and Nutrition disorders		
Anorexia	16	1
Decreased appetite	8	<1
Dehydration	3	<1
Hyperkalemia	2	<1
Hypocalcemia	1	<1
Hypokalemia	3	2
Hypomagnesemia	2	0
Hyponatremia	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		
Cough	3	0
Dyspnoea	5	<1
Epistaxis	2	<1
Exertional dyspnoea	2	<1
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		
Arthralgia	4	<1
Muscle spasms	2	0
Muscular weakness	2	0
Musculoskeletal chest pain	1	0
Musculoskeletal pain	1	0
Myalgia	3	0
Pain in extremity	5	0
Reproductive system and breast disorders		
Scrotal erythema	1	<1
General disorders and administration site conditions		
Asthenia	16	5
Chills	4	0
Fatigue	27	5
Hyperthermia	2	<1
Influenza like illness	3	<1
Malaise	3	0
Peripheral edema	4	0
Pyrexia	18	<1
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 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 adverse reaction 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 <1000/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 <1000/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 *Ovarian cancer patients* above).

Other frequent (≥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 pains, 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 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 (PPE) is characterised by painful, macular reddening skin eruptions. In patients experiencing this event, it is generally seen after two or three cycles of treatment. 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, by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight fitting). PPE appears to be dose and schedule-related and can be reduced by extending the CAELYX® dose interval 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 460mg/m^2 indicate no evidence of anthracycline-induced cardiomyopathy. The recommended dose of CAELYX® for AIDS-KS patients is 20mg/m^2 every two-to-three weeks. The cumulative dose at which cardiotoxicity would become a concern for these AIDS-KS patients (>400mg/m^2) would require more than 20 courses of CAELYX® therapy over 40 to 60 weeks.

In addition, endomyocardial biopsies were performed in 8 solid 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 trial versus doxorubicin, 10/254 patients randomized to receive CAELYX® (treated at a dose of 50 mg/m^2/every 4 weeks) versus 48/255 patients randomized to receive doxorubicin (treated at a dose of 60 mg/m^2/every 3 weeks) met the protocol-defined criteria for cardiac toxicity during treatment and/or follow-up. Cardiac toxicity was defined as a decrease of 20 points or greater from baseline if the resting LVEF remained in the normal range or a decrease of 10 points or greater if the LVEF became abnormal (less than the lower limit for normal).

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.

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

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 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 reactions identified during the postmarketing experience with CAELYX® are described below. The frequencies are provided according to the following convention:

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

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*).

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 hospitalisation, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

PHARMACOLOGICAL 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 tumours than in normal skin. Pegylated liposomes contain surface-grafted segments of the hydrophilic polymer methoxypolyethylene glycol (MPEG). These linear MPEG groups extend from the liposome surface creating a protective coating that reduces interactions between the lipid bilayer membrane and the plasma components. This allows the CAELYX® liposomes to circulate for prolonged periods in the blood stream.

Pharmacodynamic Properties

Pegylated liposomes are small enough (average diameter of approximately 100nm) to pass intact (extravasate) through defective blood vessels supplying tumours. Evidence of penetration of pegylated liposomes from blood vessels and their entry and accumulation in tumours has been seen in mice with C-26 colon carcinoma tumours and in transgenic mice with KS-like lesions. The pegylated liposomes also have a low permeability lipid matrix and internal aqueous buffer system that combine to keep doxorubicin HCl encapsulated during liposome residence time in circulation.

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

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

Mechanism of Action

The exact mechanism of the antitumour activity of doxorubicin is not known. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic 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 studies

Breast Cancer

A phase III randomized study of CAELYX® versus doxorubicin hydrochloride in patients with metastatic breast cancer was completed in 509 patients. The protocol-specified objective of demonstrating non-inferiority between CAELYX® and doxorubicin was met: 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 analysed, including those patients ≥ 55 years of age (n=166), there was a consistent treatment effect with PFS favouring CAELYX® over the active comparator (all HRs were >1.00).

Ovarian Cancer

A phase III comparative study of CAELYX® versus topotecan in patients with epithelial ovarian cancer following failure of first-line, platinum based chemotherapy was completed in 474 patients. The results of the study for evaluable patients demonstrate superiority of CAELYX® over topotecan (HR** of 1.262, 90% CI 1.062-1.500, p=0.026) for the protocol-specified primary endpoint of time to progression. For the entire ITT population, overall survival for CAELYX® was at least equivalent to topotecan with a HR of 1.121 (90% CI 0.920-1.367, p=0.34) in favour of CAELYX®.

Both time to progression and overall survival were significantly in favor of CAELYX® (time to progression: HR of 1.349, p=0.037, 90% CI 1.065-1.709, median 202 days vs. 163 days; overall survival: HR of 1.720, 90% CI 1.222-2.422, p<0.01, median 756 days vs. 498 days) in the protocol-defined platinum-sensitive subgroups in the ITT population.

When quality of life outcomes such as toxicity and progression are considered, CAELYX® is always preferred over topotecan as demonstrated in the quality-adjusted survival analysis. Although pain secondary to palmar-plantar erythrodysesthesia (PPE) is more common in CAELYX® treated patients, this rarely resulted in study discontinuation.

A consistent trend favoring CAELYX® was demonstrated across efficacy endpoints and prognostic subgroups.

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

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/m^2 (n=23)		
Maximum Plasma Concentration# (mcg/mL)	8.34	±	0.49
Plasma Clearance (L/h/m^2)	0.041	±	0.004
Volume of Distribution (L/m^2)	2.72	±	0.120
AUC (mcg/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

Kaposi's sarcoma lesion and normal skin biopsies were obtained 48 and 96 hours post-infusion. In patients receiving 20mg/m^2 CAELYX® the concentration of total (liposome encapsulated and unencapsulated) doxorubicin in the KS lesions was a median of 19 (range 3-53) times higher than in normal skin at 48 hours post-treatment.

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 HCl. With CAELYX®, the encapsulation of doxorubicin HCl 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 Reactions*).

Anaphylactoid response

During repeat dose toxicology studies in dogs, an acute response characterised by hypotension, pale mucous membranes, salivation, emesis and periods of hyperactivity followed by hypoactivity and lethargy was observed following administration of pegylated liposomes (placebo). A similar, but less severe response was also noted in dogs treated with CAELYX® or standard doxorubicin. The hypotensive response was reduced in magnitude by pre-treatment 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 relatively less local irritation or damage to the tissue after a possible extravasation.

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 toxicity

CAELYX® resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36mg/kg. Decreased testicular weights and hypospermia were present in rats after repeat doses ≥0.25mg/kg/day and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis were observed in dogs after repeat doses of 1mg/kg/day.

PHARMACEUTICAL INFORMATION

List of Excipients

α-[2-[1,2-distearoyl-sn-glycero(3)phosphooxy]ethylcarbamoyl]-ω-methoxypoly(oxyethylen)-40 sodium salt (MPEG-DSPE)
Fully Hydrogenated Soy Phosphatidylcholine (HSPC)
Cholesterol
Ammonium Sulfate
Sucrose
Histidine
Water for Injection
Hydrochloric Acid
Sodium Hydroxide

Incompatibilities

DO NOT MIX WITH OTHER DRUGS.

Shelf Life

Please refer to Outer Carton.

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

Unopened vials of material should be stored at 2ºC to 8ºC. Do not freeze. After dilution with Dextrose 5% in Water for Intravenous Infusion, the diluted CAELYX® should be used immediately. Diluted product not for immediate use should be stored at 2ºC to 8ºC for no longer than 24 hours. Partially used vials should be discarded.

Keep out of reach of children.

Nature and Contents of Container

Type I glass vials, each with a siliconized 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.

Not all pack sizes may be marketed.

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® 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 of 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**.

BATCH RELEASER

Janssen Pharmaceutica N.V.
Turnhoutseweg 30
B-2340 Beerse, Belgium

Product Registrant:
Baxter Healthcare (Asia) Pte. Ltd.
150 Beach Road, #30-01/08, Gateway West
Singapore 189720

DATE OF REVISION OF THE TEXT
Jul 2021 (CCDS 05 February 2020)

**Hazard ratio is the ratio of failure rates between 2 treatments, i.e., the hazard ratio of 1.262 for time to progression for topotecan relative to CAELYX® means there is a 26.2% higher probability of disease progression on topotecan relative to CAELYX® throughout the study.

Baxter Global Labeling

Baxter

Baxter Tel.: +1 (224) 270-4652
E-mail: gary_berman@baxter.com

Insert CAELYX
PCC **745503**

Format Ref:	B/I/045/V1 540x340 (folded 60x34)
Tech. info/Spec:	N/A
Country:	SG
Mat. ID Code:	1312
File Name:	745503_02SEP2021.indd
Font Type:	Helvetica World
Font Size:	7 pt

Times New Roman compared to our standard fonts

Times New Roman	Helvetica World	Antique Olive	Futura	Karbon
6 pt xxx	5.2 pt xxx	4.3 pt xxx	5.8 pt xxx	6.2 pt xxx
7 pt xxx	6 pt xxx	5.1 pt xxx	6.7 pt xxx	7.2 pt xxx
8 pt xxx	6.9 pt xxx	5.8 pt xxx	7.7 pt xxx	8.2 pt xxx
9 pt xxx	7.7 pt xxx	6.5 pt xxx	8.6 pt xxx	9.2 pt xxx

■ Black

Date	*(Designer)*
1. 27-JUL-21	(GSB)
2. 18-AUG-21	(GSB)
3. 23-AUG-21	(GSB)
4. 02-SEP-21	(GSB)