PRODUCT MONOGRAPH

CAELYX®

Pegylated Liposomal Doxorubicin Hydrochloride for Injection

Sterile aqueous suspension for intravenous administration
(2 mg/mL)

Antineoplastic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Injection	2 mg/mL	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

CAELYX® (Pegylated Liposomal Doxorubicin Hydrochloride for Injection) is indicated for:

- monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk associated with conventional doxorubicin.
- advanced ovarian carcinoma in women who have failed standard first-line therapy. Platinum-and paclitaxel- based chemotherapy is the current standard first-line treatment regimen.
- AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (<200 CD4 lymphocytes/mm^3) and extensive mucocutaneous or visceral disease whose disease has progressed despite therapy or who are intolerant to prior systemic combination chemotherapy comprising of at least two of the following agents: a vinca alkaloid, bleomycin and doxorubicin (or another anthracycline).

CONTRAINDICATIONS

- CAELYX® is contraindicated in patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin hydrochloride or the components of CAELYX®.
- Should not be administered while breast-feeding.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Cardiotoxicity including congestive heart failure and cardiomyopathy may occur (See WARNINGS AND PRECAUTIONS/Cardiovascular);**
- **Acute infusion reactions (see General/Infusion Reactions);**
- **Myelosuppression (see WARNINGS AND PRECAUTIONS/Hematologic/Myelosuppression);**
- **Secondary oral neoplasms including fatal cases (see WARNINGS AND PRECATIONS/Second Primary Malignancies)**
- **CAELYX® should only be administered by physicians experienced with cancer chemotherapeutic drugs.**

General

CAELYX® is a unique formulation of doxorubicin hydrochloride and must not be used interchangeably with other formulations of doxorubicin hydrochloride.

Infusion Reactions

Serious and sometimes life-threatening infusion reactions may occur within minutes of starting the infusion of CAELYX®. These reactions have been described as allergic-like or anaphylactoid-like and are 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. Very rarely, convulsions have been observed in relation to infusion reactions.

Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medication 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-associated 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**).

In patients with solid tumors, 100 out of 929 patients (10.8%) were described as having an infusion-associated reaction during treatment with CAELYX®. Permanent treatment discontinuation rates were infrequently reported at 2%.

In the pivotal breast cancer trials, a similar incidence of infusion reactions 32/254 (13%) was observed. The rate of permanent treatment discontinuation was 2% (4/254).
In the ovarian cancer population (subset of the solid tumor cohort), 51/510 (10%) patients reported treatment-related infusion reaction adverse events. Five patients (<1%) (reporting nine events) discontinued due to treatment-related infusion reactions.

In patients with AIDS-KS, infusion-associated reactions were characterized by flushing, shortness of breath, facial edema, headache, chills, back pain, tightness in the chest and throat and/or hypotension and can be expected at the rate of 5% to 10%. Very rarely, convulsions have been observed in relation to infusion reactions. Many patients were able to tolerate further infusions without complications, however, eight patients discontinued CAELYX® therapy because of an infusion reaction.

Injection Site Effects
CAELYX® should be considered an irritant and precautions should be taken to avoid extravasation (see **DOSAGE AND ADMINISTRATION**).

In studies with rabbits, lesions that were induced by subcutaneous injection of CAELYX® were minor and reversible compared to more severe and irreversible lesions and tissue necrosis that were induced after subcutaneous injection of conventional doxorubicin hydrochloride.

Toxicity Potentiation
The doxorubicin in CAELYX® may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with the conventional formulation of doxorubicin hydrochloride. Radiation-induced toxicity to the myocardium, mucosae, skin and liver has been reported to be increased by the administration of doxorubicin hydrochloride.

Cardiovascular
Special attention must be given to the cardiac toxicity exhibited by doxorubicin hydrochloride. Although uncommon, acute left ventricular failure has occurred, particularly in patients who have received a total dosage of doxorubicin exceeding the currently recommended limit of 550 mg/m^2 body surface. This limit appears to be lower (400 mg/m^2 body surface) in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. The incidence of CAELYX®-associated cardiotoxicity was significantly lower than that with conventional doxorubicin hydrochloride.

Caution should be observed in patients who have received other anthracyclines or anthracenediones. The total dose of doxorubicin HCl administered to the individual patient should also take into account any previous or concomitant therapy with related compounds such as daunorubicin. Congestive heart failure and/or cardiomyopathy may be encountered after discontinuation of therapy.

Patients with a history of cardiovascular disease should be administered CAELYX® only when the potential benefit of treatment outweighs the risk.

Cardiac function, particularly left ventricular ejection fraction (LVEF) should be monitored at baseline and periodically by MUGA scan or echography. The evaluation of left ventricular function is considered to be mandatory before each additional administration of CAELYX® that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2 body surface.

Congestive heart failure and/or cardiomyopathy may occur suddenly, without prior ECG changes and may also be encountered several weeks after discontinuation of therapy.

Hematologic

Myelosuppression

In AIDS-KS and other patient populations treated with CAELYX®, many patients presented with baseline myelosuppression due to such factors as their HIV disease, numerous concomitant medications, or tumors involving bone marrow. In the AIDS-KS population, myelosuppression appears to be the dose-limiting adverse event. Leukopenia is the most common adverse event (about 60%) experienced in this population; anemia (about 20%) and thrombocytopenia (about 10%) can also be expected.

In patients with ovarian cancer treated at a dose of 50 mg/m^2 body surface, myelosuppression was generally mild to moderate, reversible, and was not associated with episodes of neutropenic infection or sepsis. A similar low incidence of myelosuppression was seen in patients with metastatic breast cancer receiving CAELYX® in a first-line clinical trial, although febrile neutropenia was seen in 3/254 (1.2 %) patients receiving CAELYX® 50 mg/m^2 body surface, every 4 weeks.

Leukopenia (33.2%) was the most frequently reported hematological adverse event, followed by anemia (32.2%), neutropenia (31.6%) and thrombocytopenia (10.7%). Life-threatening (Grade IV) hematological effects were extremely rare (1.6%, 0.4%, 2.9% and 0.2% respectively). Growth factor support was required infrequently (<5%) and transfusion support was required in approximately 15% of patients.

Because of this potential for bone marrow suppression, careful hematologic monitoring is required during use of CAELYX®. Complete blood counts, including platelet counts, should be obtained frequently and at a minimum prior to each dose of CAELYX®. With the recommended dosage schedule, leukopenia is usually transient. Hematologic toxicity may require dose reduction or suspension or delay of CAELYX® therapy.

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

CAELYX® may potentiate the toxicity of other anticancer therapies. In particular, hematologic toxicity may be more severe when CAELYX® is administered in combination with other agents that cause bone marrow suppression. Patients treated with CAELYX® may require growth factors to support their blood counts.

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 or CAELYX® should be kept under hematologic supervision.

Hepatic/Biliary/Pancreatic

The pharmacokinetics of CAELYX® have not been studied in patients with hepatic impairment. Doxorubicin is known to be eliminated in large part by the liver. Thus CAELYX® dosage should be reduced in patients with impaired hepatic function (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**). Prior to CAELYX® administration, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin.

Diabetics
Precautions should be taken when using CAELYX® in diabetics, since CAELYX® is diluted in a (5%) Dextrose Injection USP solution.

Skin
Palmar-Plantar Erythrodysesthesia (PPE)
In 254 breast cancer patients treated with CAELYX® at a dose of 50 mg/m^2 body surface, every 4 weeks, 42 patients (17%) reported Grade III PPE, and no cases of Grade IV PPE were reported. Discontinuations due to PPE were infrequent (17 patients, 7%).

In 512 ovarian cancer patients treated with CAELYX® at a dose of 50 mg/m^2 body surface, 100 patients (19.5%) reported Grade III treatment-related PPE and 3 patients (0.6%) reported Grade IV treatment-related PPE, with 19 patients (3.7%) discontinuing.

In 705 patients with AIDS-related Kaposi's sarcoma treated with CAELYX® at 20 mg/m^2 body surface, 24 patients (3.4%) developed PPE with 3 patients (0.9%) discontinuing.

Palmar-plantar erythrodysesthesia is characterized by painful, macular reddening skin eruptions, swelling, and, for some patients, desquamation of the skin on the hands and the feet.

PPE was generally seen after 2 or 3 cycles of treatment but may occur earlier. In most patients the reaction is mild and resolves in one to two weeks with or without treatment with corticosteroids so that prolonged delay of therapy need not occur. However, dose modification may be required to manage PPE (see **DOSAGE AND ADMINISTRATION**, **Dose Modifications**). The reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

Strategies to prevent and treat PPE include keeping hands and feet cool by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight-fitting). PPE appears to be primarily related to the dose schedule and can be reduced by extending the CAELYX® dose interval 1-2 weeks or reducing the CAELYX® dose. In some settings, pyridoxine has been tried to ameliorate the symptoms of PPE.

Radiation Therapy
Skin recall reaction due to prior radiotherapy has occurred with CAELYX® administration.

Second Primary Malignancies
Oral Neoplasms
Cases of secondary oral cancer (including fatalities) have been reported in patients exposed to CAELYX®. 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 (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Special Populations

Pregnant Women

CAELYX® should not be administered to pregnant women. Women of childbearing 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.

CAELYX® can cause fetal harm when administered to pregnant women. CAELYX® is embryotoxic in rat and embryotoxic and abortifacient in rabbits. Teratogenicity cannot be ruled out.

Nursing Women

It is not known whether this drug is excreted in human milk. Due to the potential for serious adverse reactions in nursing infants from CAELYX®, mothers should discontinue nursing prior to taking this drug.

Pediatrics

The safety and effectiveness of CAELYX® in pediatric patients have not been established.

Geriatrics (>60 years of age)

Experience with CAELYX® in patients over 60 years of age is limited **(**see **ACTION AND CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Breast Cancer

Breast Cancer Patients: 254 patients with advanced breast cancer who had not received prior chemotherapy for metastatic disease were treated with CAELYX® at a dose of 50 mg/m^2 body surface, every 4 weeks in a phase III clinical trial. The most frequently reported treatment-related adverse effects included palmar-plantar erythrodysesthesia (PPE) (48.0%) and nausea (37.0%) (Table 1). 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, 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). Febrile neutropenia was reported in 3/254 (1.2%) patients treated with CAELYX® and 8/255 (3.1%) patients treated with doxorubicin.

Laboratory Abnormalities: 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%). No clinically significant increases in serum creatinine were reported. Clinically significant hematologic measurements were infrequent and low as measured by leukopenia (4.3%), anemia (3.9%), neutropenia (1.6%) and thrombocytopenia (1.2%). Sepsis was reported at an incidence of 1%.

Table 1 - Treatment-related Undesirable Effects Reported in ≥5% of CAELYX® -treated Patients by Severity and Body System in Breast Cancer Clinical Trial (I97-328).

AE body system	I97-328 All severities %	I97-328 Grades III/IV %
Body as a Whole		
Asthenia	10	1
Erythema	7	<1
Fatigue	12	<1
Fever	8	0
Weakness	6	<1
Gastro-intestinal System		
Abdominal Pain	8	1
Anorexia	11	1
Constipation	8	<1
Diarrhea	7	1
Mouth Ulceration	5	<1
Mucositis Nose	23	4
Nausea	37	3
Stomatitis	22	5
Vomiting	19	<1
Red Blood Cell Disorders		
Anemia	5	1
Skin and Appendages		
Alopecia	20	0
PPE*	48	17
Pigmentation abnormal	8	<1
Rash	10	2

* Palmar-plantar erythrodysesthesia (hand- foot syndrome). No cases of Grade IV (life-threatening) PPE were reported.

Undesirable effects reported between ≥1% and <5% in 254 CAELYX®-treated breast cancer patients, not previously reported in CAELYX® clinical trials were breast pain, leg cramps, edema, leg edema, peripheral neuropathy, oral pain, ventricular arrhythmia, folliculitis, bone pain, musculo-skeletal pain, thrombocythemia, cold sores (non-herpetic), fungal infection, epistaxis, upper respiratory tract infection, bullous eruption, dermatitis, erythematous rash, dry

skin, pruritus, skin discoloration, scaly skin, nail disorder, lacrimation, blurred vision, flushing, weight decrease, dyspepsia and dyspnea.

Ovarian Cancer

Ovarian Cancer Trials (Phase II and III)
Information on the adverse reactions is based on the experience in 512 patients with ovarian cancer treated at a dose of 50 mg/m^2 body surface. The median cumulative dose in the ovarian cancer trials was 150.6 mg/m^2, median cycle length was 30.0 days, and median days on drug was 65.5 days.

Of these 512 patients, a total of 509 patients (99.4%) in the ovarian cancer trials, reported a total of 5026 adverse events, and 484 (94.5%) patients reported treatment-related adverse events. Treatment-related fatal adverse events were reported in 4 (0.8%) patients, while Grade IV (life-threatening) treatment-related adverse events were reported by 38 (7.4%) patients.

Myelosuppression was mostly mild or moderate and manageable. Leukopenia (33.2%) was the most frequently reported hematological adverse event, followed by anemia (32.2%), neutropenia (31.6%) and thrombocytopenia (10.7%). Life-threatening (Grade IV) haematological effects were extremely rare (1.6%, 0.4%, 2.9% and 0.2%, respectively). Growth factor support was required infrequently (<5%) and transfusion support was required in approximately 15% of patients.

Frequently reported treatment-related adverse effects included palmar-plantar erythrodysesthesia (PPE) (46.1%) and stomatitis (38.9%). 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).

Other frequently reported drug-related effects (≥5%) included nausea (38.1%), asthenia (34.0%), rash (25.0%), vomiting (24.4%), alopecia (17.4%), constipation (12.9%), anorexia (12.1%), mucous membrane disorder (14.5%), diarrhea (11.7%), abdominal pain (8.2%), fever (9.4%), paresthesia (7.6%), pain (7.4%), skin discoloration (6.1%), pharyngitis (6.4%), dry skin (5.9%), dyspepsia (5.5%) and somnolence (5.1%).

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.

Table 2 - Summary of Frequently Reported (≥1%) Treatment-related Adverse Events by Severity (Grade III/IV), Body System and COSTART Preferred Term Reported in Ovarian Cancer Patients			
Adverse Event	**Ovarian Cancer Patients treated with CAELYX® n=512**		
No. (%) of Patients Reporting Treatment-related Adverse Events	**n=484 (94.5%)**		
	Grade III	**Grade IV**	**All Severities**
Body as a Whole			
Asthenia	34 (6.6)	0	174 (34.0)
Mucous Membrane Disorder	16 (3.1)	0	74 (14.5)
Digestive System			
Stomatitis	41 (8.0)	5 (0.8)	199 (38.9)
Nausea	21 (4.1)	1 (0.2)	195 (38.1)
Vomiting	22 (4.3)	3 (0.6)	125 (24.4)
Hemic and Lymphatic System			
Leukopenia	36 (7.0)	8 (1.6)	170 (33.2)
Anemia	28 (5.5)	2 (0.4)	165 (32.2)
Neutropenia	46 (9.0)	15 (2.9)	162 (31.6)
Thrombocytopenia	6 (1.2)	1 (0.2)	55 (10.7)
Skin and Appendages			
Hand-Foot Syndrome*	100 (19.5)	3 (0.6)	236 (46.1)
Rash	17 (3.3)	1 (0.2)	128 (25.0)
Alopecia	6 (1.2)	0	89 (17.4)

*Palmar-plantar erythrodysesthesia (PPE)

Laboratory Abnormalities: In the subset of 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%).

Pivotal Phase III Trial - Ovarian Cancer

In the pivotal phase III ovarian cancer trial, the toxicity profiles of the two agents, CAELYX® and topotecan were very different.

Hematologic toxicity was more frequent and usually Grade III, IV in the topotecan-treated patients in comparison with CAELYX® (neutropenia 77% vs 12%, thrombocytopenia 34% vs 1%, and anemia 28% vs 5% respectively). Grade III, IV hematologic adverse events were observed in 90% of topotecan-treated patients compared with 55% of CAELYX®-treated patients.

Most drug-related adverse events associated with CAELYX® were mild to moderate in severity with the exceptions of palmar-plantar erythrodysesthesia (PPE) and stomatitis. However, PPE and stomatitis were managed successfully with dose modifications and rarely resulted in study discontinuation (4% for PPE and 1% for stomatitis).

There was no evidence of a relationship between cumulative CAELYX® dose and change from baseline for LVEF (left ventricular ejection fraction).

Topotecan-associated toxicities more often resulted in morbidity and life-threatening sequelae than the primary CAELYX®-related adverse events.

In the pivotal phase III ovarian cancer study, comparing CAELYX® vs. topotecan, three deaths in the topotecan group due to neutropenic sepsis were considered treatment-related. There were no treatment-related deaths in the CAELYX® group. There were no cases of treatment-related sepsis or neutropenic fever in the CAELYX® group.

Table 3 – Treatment-Related Adverse Events Reported by >10% of Patients in Either Ovarian Cancer Treatment Group (Pivotal Phase III Study)

Any Adverse Event	CAELYX® (n=239)			Topotecan (n=235)		
	All Grades	Grade III	Grade IV	All Grades	Grade III	Grade IV
	222 (93%)	132 (55%)	20 (8%)	232 (99%)	176 (75%)	158 (67%)
Body as a whole						
Asthenia	75 (31%)	13 (5%)	0	104 (44%)	17 (7%)	0
Mucous membrane disorder	33 (14%)	8 (3%)	0	7 (3%)	0	0
Fever	28 (12%)	0	0	49 (21%)	6 (3%)	5 (2%)
Abdominal pain	20 (8%)	3 (1%)	0	29 (12%)	3 (1%)	1 (<1%)
Digestive System						
Stomatitis	95 (40%)	19 (8%)	1 (<1%)	35 (15%)	1 (<1%)	0
Nausea	85 (36%)	6 (3%)	1 (<1%)	127 (54%)	12 (5%)	2 (1%)
Vomiting	58 (24%)	11 (5%)	2 (1%)	81 (35%)	14 (6%)	2 (1%)
Constipation	33 (14%)	0	0	58 (25%)	3 (1%)	1 (<1%)
Diarrhea	28 (12%)	4 (2%)	0	49 (21%)	5 (2%)	1 (<1%)
Anorexia	26 (11%)	1 (<1%)	0	32 (14%)	1 (<1%)	0
Hematopoietic and Lymphatic System						
Leukopenia	87 (36%)	21 (9%)	3 (1%)	149 (63%)	82 (35%)	35 (15%)
Anemia	85 (36%)	12 (5%)	1 (<1%)	169 (72%)	58 (25%)	8 (3%)
Neutropenia	84 (35%)	19 (8%)	10 (4%)	191 (81%)	33 (14%)	145 (62%)
Thrombocytopenia	31 (13%)	3 (1%)	0	152 (65%)	40 (17%)	40 (17%)
Skin and Appendages						
PPE*	117 (49%)	53 (22%)	2 (1%)	2 (1%)	0	0
Rash	58 (24%)	10 (4%)	0	18 (8%)	1 (<1%)	0
Alopecia	38 (16%)	3 (1%)	0	115 (49%)	14 (6%)	0

* Palmar-plantar erythrodysesthesia

AIDS-KS

Information on adverse events is based on the experience reported in 711 patients with AIDS-KS enrolled in four open-label studies, as well as 254 patients enrolled in two controlled trials. The majority of patients were treated with 20 mg/m^2 (body surface) of CAELYX® every two to three weeks.

Open-label trials

In the open-label trials, the median cumulative dose of CAELYX® (Pegylated Liposomal Doxorubicin Hydrochloride for Injection) was 120 mg/m^2 body surface. Overall, the immune status was poor in 90.1% of the patients enrolled in these studies, with a median CD4 count of 20 cells/mm^3.

As expected, patients were receiving many concomitant medications. Over half (58.1%) of the patients were taking one of the four available antiretroviral medications; zidovudine (AZT) was the most frequently employed in 34.3% of patients, with didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) also used in decreasing order of frequency. Use and frequency of other antivirals was frequent: 55.7% received acyclovir at sometime during the trial, 28.9% received ganciclovir and 16.4% received foscarnet. Systemic antifungals were frequently employed with fluconazole being used by 75.7% of patients. Prophylactic therapy of opportunistic infections was used; sulfamethoxazole/trimethoprim being used the most, in 54.9% of patients.

In many instances, it was difficult to determine whether adverse events resulted from CAELYX®, from concomitant therapy, or from the patients' underlying disease(s). Of the 711 patients for whom adverse events data are recorded, 84.6% reported one or more adverse events that were considered by the investigators to be possibly related, probably related or related to treatment with CAELYX®. For patients who discontinued therapy, death was the most common reason (32.3% of patients). Adverse reactions only infrequently (5.3%) led to discontinuation of treatment.

Controlled trials

In the two controlled studies, the median dose of CAELYX® administered per cycle was 20mg/m^2 body surface, and the mean duration of therapy with CAELYX® was 81.1 days. The majority of patients were classified as poor risk. In all three groups, subcutaneous KS lesions were present in more than 98.4% of patients; 21.7% of patients had evidence of pulmonary KS; and 15.7% of patients had evidence gastrointestinal involvement. In all of the three groups, the majority of patients had CD4 cell counts of less than 50 cells/mm^3.

Fewer CAELYX®-treated patients died during the course of the controlled trials (16.9%). Early termination due to adverse events was observed in 10.6% of CAELYX®-treated patients. In general, the safety profile of the patients treated in the controlled studies was consistent with the safety profile of the patients that were treated with CAELYX® in the open-label trials. Opportunistic infections, such as candidiasis (47.8%), cytomegalovirus (37.5%), *Pneumocystis carinii* pneumonia (20.6%), and *Mycobacterium avium* complex (10.1%), regardless of causality, have been frequently observed in patients with AIDS-KS receiving CAELYX®. The table below shows all events occurring at ≥5% in the open-label and controlled trials, that were considered by investigators, at least possibly related to the study drug.

Table 4 - Possibly or Probably Drug-Related Adverse Events by Body System and Costart Preferred Term Including Open Label Studies - Reported in ≥5% of AIDS-KS Patients.				
	CAELYX® (Open Label)[1]	**CAELYX® (Comparator)[2]**	**ABV[3]**	**BV[4]**
Number of Patients	711	254	125	120
Number of Patients Reporting Adverse Events	566 (79.6%)	192 (75.6%)	114 (91.2%)	92 (76.7%)
Number of Patients by Body System and Preferred COSTART Term Incidence				
Body as a whole	**165 (23.2%)**	**55 (21.7%)**	**72 (57.6%)**	**43 (35.8%)**
asthenia	67 (9.4%)	29 (11.4%)	37 (29.6%)	10 (8.3%)
fever	62 (8.7%)	13 (5.1%)	38 (30.4%)	22 (18.3%)
headache	30 (4.2%)	7 (2.8%)	9 (7.2%)	4 (3.3%)
abdominal pain	16 (2.3%)	3 (1.2%)	7 (5.6%)	1 (0.8%)
chills	8 (1.1%)	2 (0.8%)	8 (6.4%)	6 (5.0%)
pain	10 (1.4%)	3 (1.2%)	7 (5.6%)	2 (1.7%)
lab test abnormal	3 (0.4%)	8 (3.1%)	0	7 (5.8%)
chills and fever	2 (0.3%)	2 (0.8%)	6 (4.8%)	6 (5.0%)
malaise	3 (0.4%)	2 (0.8%)	6 (4.8%)	1 (0.8%)
Cardiovascular system	**2 (0.3%)**	**1 (0.4%)**	**6 (4.8%)**	**1 (0.8%)**
phlebitis	2 (0.3%)	1 (0.4%)	6 (4.8%)	1 (0.8%)
Digestive system	**207 (29.1%)**	**57 (22.4%)**	**77 (61.6%)**	**37 (30.8%)**
nausea	91 (12.8%)	36 (14.2%)	54 (43.2%)	14 (11.7%)
diarrhea	53 (7.5%)	10 (3.9%)	11 (8.8%)	3 (2.5%)
stomatitis	45 (6.3%)	12 (4.7%)	4 (3.2%)	2 (1.7%)
nausea and vomiting	29 (4.1%)	2 (0.8%)	15 (12.0%)	10 (8.3%)
vomiting	25 (3.5%)	8 (3.1%)	17 (13.6%)	3 (2.5%)
oral moniliasis	40 (5.6%)	2 (0.8%)	2 (1.6%)	4 (3.3%)
anorexia	8 (1.1%)	6 (2.4%)	17 (13.6%)	3 (2.5%)
constipation	12 (1.7%)	2 (0.8%)	8 (6.4%)	9 (7.5%)
Hemic and lymphatic system	**471 (66.2%)**	**144 (56.7%)**	**63 (50.4%)**	**49 (40.8%)**
leukopenia	435 (61.2%)	138 (54.3%)	56 (44.8%)	46 (38,3%)
anemia	145 (20.4%)	19 (7.5%)	14 (11.2%)	9 (7.5%)
thrombocytopenia	66 (9.3%)	15 (5.9%)	6 (4.8%)	12 (10.0%)
hypochromic anemia	68 (9.6%)	9 (3.5%)	6 (4.8%)	6 (5.0%)
Nervous system	**15 (2.1%)**	**10 (3.9%)**	**30 (24.0%)**	**28 (23.3%)**
paresthesia	6 (0.8%)	6 (2.4%)	14 (11.2%)	14 (11.7%)
neuropathy	4 (0.6%)	3 (1.2%)	9 (7.2%)	11 (9.2%)
peripheral neuritis	6 (0.8%)	2 (0.8%)	10 (8.0%)	5 (4.2%)
Skin and appendages	**81 (11.4%)**	**30 (11.8%)**	**55 (44.0%)**	**12 (10.0%)**
alopecia	63 (8.9%)	18 (7.1%)	53 (42.4%)	10 (8.3%)
rash	19 (2.7%)	12 (4.7%)	5 (4.0%)	2 (1.7%)

1. Patients treated with CAELYX® in the open-label studies.
2. Patients treated with CAELYX® in the controlled studies (vs. ABV or BV).
3. ABV (adriamycin, bleomycin, vincristine)
4. BV (bleomycin, vincristine)

Incidence 1% to 5% (Possibly or Probably Related) in CAELYX®-treated AIDS-KS Patients

Body as a Whole: allergic reaction, anaphylactoid reaction, back pain, chest pain, flu syndrome, infection, mucous membrane disorder, pain.

Cardiovascular: hypotension, tachycardia, vasodilatation.

Digestive System: aphthous stomatitis, dyspepsia, dysphagia, glossitis, liver function tests abnormal, mouth ulceration.

Hemic and Lymphatic System: hemolysis, pancytopenia, prothrombin increased.

Metabolic/Nutritional: bilirubinemia, SGOT increased, SGPT increased, weight loss.

Nervous System: dizziness, emotional lability, somnolence.

Respiratory System: dyspnea, pneumonia.

Skin and Appendages: dry skin, herpes simplex, pruritus.

Others: retinitis, albuminuria.

Incidence Less Than 1% (Possibly or Probably Related) in CAELYX®-Treated AIDS-KS Patients

Body As A Whole: abscess, cellulitis, substernal chest pain, cryptococcosis, facial edema, hypothermia, immune system disorder, injection site hemorrhage, injection site pain, injection site reaction, moniliasis, neoplasm, radiation injury, sepsis.

Cardiovascular System: arrhythmia, bradycardia, bundle branch block, cardiomegaly, cardiovascular disorder, congestive heart failure, deep thrombophlebitis, heart failure, hemorrhage, migraine, palpitation, pericardial effusion, peripheral vascular disorder, supraventricular extrasystoles, syncope, thrombophlebitis, thrombosis, ventricular arrhythmia, ventricular extrasystoles.

Digestive System: bloody diarrhea, cholestatic jaundice, colitis, dry mouth, eructation, esophageal ulcer, esophagitis, fecal impaction, gastritis, GI hemorrhage, gingivitis, hematemesis, hepatic failure, hepatitis, hepatosplenomegaly, increased appetite, jaundice, leukoplakia of mouth, liver damage, melena, pancreatitis, rectal disorder, sclerosing cholangitis, tenesmus, ulcerative proctitis, ulcerative stomatitis.

Endocrine System: diabetes mellitus.

Hemic and Lymphatic System: eosinophilia, erythrocytes abnormal, lymphadenopathy, lymphangitis, lymphedema, lymphoma-like reaction, marrow depression, petechia, purpura, thromboplastin decreased.

Metabolic/Nutritional: BUN increased, cachexia, creatinine increased, dehydration, edema, hypercalcemia, hyperkalemia, hyperlipemia, hypernatremia, hyperphosphatemia, hyperuricemia, hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypoproteinemia, ketosis, LDH increased, peripheral edema, weight gain.

Musculoskeletal System: arthralgia, bone disorder, bone pain, joint disorder, myalgia, myasthenia, myositis.

Nervous System: abnormal dreams, abnormal gait, acute brain syndrome, anxiety, cerebrovascular accident, confusion, convulsion, depression, dysarthria, dyskinesia, hypertonia, hypokinesia, hypotonia, insomnia, nervousness, nystagmus, paralysis, reflexes decreased, thinking abnormal, vertigo.

Respiratory System: asthma, bronchitis, cough increased, hiccup, hyperventilation, lung disorder, pharyngitis, pleural effusion, pneumothorax, rhinitis, sinusitis.

Skin and Appendages: acne, cutaneous moniliasis, eczema, erythema nodosum, exfoliative dermatitis, furunculosis, herpes zoster, leukoderma, maculopapular rash, psoriasis, pustular rash, seborrhea, skin discoloration, skin necrosis, skin ulcer.

Special Senses: abnormal vision, blindness, conjunctivitis, diplopia, eye disorder, eye pain, optic neuritis, otitis media, taste perversion, tinnitus.

Urogenital System: balanitis, cystitis, dysuria, genital edema, glycosuria, hematuria, kidney failure, kidney function abnormal, prostatic disorder, testis disorder, urine abnormality.

Post-Market Adverse Drug Reactions

The following serious adverse reactions have been derived from spontaneous case reports, literature cases, expanded access programs, and clinical studies other than the global registration trials. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System: myelosuppression associated with anemia, thrombocytopenia, leukopenia, febrile neutropenia.

Neoplasms benign, malignant and unspecified (incl cysts and polyps): secondary oral cancer including fatal cases (see **WARNINGS AND PRECAUTIONS, Second Primary Malignancies, Oral Neoplasms**).

Nervous System: convulsions (see **WARNINGS AND PRECAUTIONS**, **General, Infusion Reactions**).

Skin and Subcutaneous Tissue: serious skin conditions including erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, lichenoid keratosis.

Vascular: thrombophlebitis, venous thrombosis, pulmonary embolism. Patients with cancer are at increased risk for thromboembolic disease.

DRUG INTERACTIONS

Overview
No formal drug interaction studies have been conducted with CAELYX®. CAELYX® may interact with drugs known to interact with the conventional formulation of doxorubicin hydrochloride.

In patients who have received concomitant cyclophosphamide or taxanes, no new additive toxicities were noted.

Drug-Food Interactions
CAELYX® interactions with food have not been established.

Drug-Herb Interactions
CAELYX® interactions with herbal products have not been established.

Drug-Laboratory Interactions
CAELYX® interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
CAELYX® (Pegylated Liposomal Doxorubicin Hydrochloride for Injection) exhibits unique pharmacokinetic properties and must not be used interchangeably with other formulations of doxorubicin hydrochloride.

Breast Cancer/Ovarian Cancer Patients
CAELYX® is administered intravenously at a dose of 50 mg/m^2 body surface, once every 4 weeks for as long as the disease does not progress, and the patient shows no evidence of clinical cardiotoxicity and continues to tolerate treatment.

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

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®.

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.

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® (see **WARNINGS AND PRECAUTIONS**). Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medications to treat these symptoms (e.g., antihistamines, corticosteroids, and adrenaline) as well as emergency equipment should be available for immediate use. In most patients treatment can be resumed after all symptoms have resolved, without recurrence. Infusion reactions rarely recur after the first treatment cycle. To minimize the risk of infusion reactions, the initial dose should be administered at a rate no greater than 1 mg/minute (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

AIDS-KS Patients
CAELYX® should be administered intravenously at a dose of 20 mg/m^2 body surface (equivalent to doxorubicin HCl) once 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 as long as they respond satisfactorily and tolerate treatment.

The appropriate dose of CAELYX® is diluted in 250 mL of (5%) Dextrose Injection USP and administered by intravenous infusion over 30 minutes. CAELYX® should not exceed 90 mg per infusion. Rapid infusion may increase the risk of infusion-related reactions (see **WARNINGS AND PRECAUTIONS**, **General**, **Infusion Reactions**). It is recommended that the CAELYX® infusion line be connected through the side port of an intravenous infusion of (5%) Dextrose USP Intravenous Infusion to achieve further dilution and minimize the risk of thrombosis and extravasation.

CAELYX® should be considered an irritant and precautions should be taken to avoid extravasation. On intravenous administration of CAELYX®, extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, 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.

DO NOT administer as a bolus injection or undiluted solution. CAELYX® must not be given by the intramuscular or subcutaneous route.

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.

Partially used vials should be discarded. CAELYX® should be handled and disposed of in a manner consistent with that of other anti-cancer drugs. There are several guidelines on this subject (see **REFERENCES**).

Incompatibilities
Until specific compatibility data are available, it is not recommended that CAELYX® be mixed with other drugs.

Dose Modifications
Dose adjustment is required in patients with a history of prior anthracycline use, prior mediastinal irradiation, concurrent cyclophosphamide therapy, and pre-existing cardiovascular disease.

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 following tables. The toxicity grading in these tables is based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

The tables for PPE and stomatitis (Table 5, Table 6) provide the schedule followed for dose modification in clinical trials in the treatment of breast cancer 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 hematological toxicity (Table 7) 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 Table 8, Table 9, and Table 10.

Guidelines for CAELYX® Dose Modification in Breast or Ovarian Cancer Patients

Table 5 - PALMAR - PLANTAR ERYTHRODYSESTHESIA		
	Week After Prior CAELYX® Dose	
Toxicity Grade At Current Assessment	**Weeks 4 & 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	Decrease dose by 25%; return to 4-week interval

Table 5 - PALMAR - PLANTAR ERYTHRODYSESTHESIA		
	Week After Prior CAELYX® Dose	
Toxicity Grade At Current Assessment	**Weeks 4 & 5**	**Week 6**
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	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	Withdraw patient
Grade -4- (diffuse or local process causing infectious complications, or a bedridden state or hospitalization)	Wait an additional week	Withdraw patient

Table 6 - STOMATITIS		
	Week after Prior CAELYX® Dose	
Toxicity Grade at Current Assessment	**Weeks 4 & 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	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	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	Withdraw patient
Grade -4- (requires parenteral or enteral support)	Wait an additional week	Withdraw patient

Table 7 - HEMATOLOGICAL TOXICITY (ANC OR PLATELETS) – MANAGEMENT OF PATIENTS WITH BREAST OR OVARIAN CANCER			
GRADE	**ANC**	**PLATELETS**	**MODIFICATION**
1	1500 - 1900	75,000 - 150,000	Resume treatment with no dose reduction.
2	1000 - <1500	50,000 - <75,000	Wait until ANC ≥1,500 and platelets ≥75,000; redose with no dose reduction.
3	500 - <1000	25,000 - <50,000	Wait until ANC ≥1,500 and platelets ≥75,000; redose with no dose reduction.
4	<500	<25,000	Wait until ANC ≥1,500 and platelets ≥75,000; decrease dose by 25% or continue full dose with growth factor support.

The dose modifications shown in the tables below are recommended for managing possible adverse events in AIDS-KS patients:

Guidelines for CAELYX® Dose Modification in AIDS-KS Patients

Table 8 - PALMAR-PLANTAR ERYTHRODYSESTHESIA			
Toxicity Grade	**Symptoms**	**Weeks Since Last Dose**	
		3	**4**
0	no symptoms	Redose at 2-to 3-week interval	Redose at 2-to 3-week interval
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 at 25% dose reduction; return to 3-week interval
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	Redose at 50% dose reduction; return to 3-week interval
3	blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	Wait an additional week	Discontinue CAELYX®
4	diffuse or local process causing infectious complications, or a bed ridden state or hospitalization		

Table 9 - HEMATOLOGICAL TOXICITY			
Grade	**ANC** (10^9 cells/L)	**Platelets** (10^9 cells/L)	**Modification**
1	1.5 - 1.9	75 - 150	None
2	1.0 - <1.5	50 - <75	None
3	0.5 - 0. 999	25 - <50	Wait until ANC ≥1.0 and/or platelets ≥50 then redose at 25% dose reduction
4	<0.5	<25	Wait until ANC≥1.0 and/or platelets ≥50 then redose at 50% dose reduction

Table 10 - STOMATITIS		
Grade	**Symptoms**	**Modification**
1	Painless ulcers, erythema, or mild soreness	None
2	Painful erythema, edema, or ulcers, but can eat	Wait one week and if symptoms improve redose at 100% dose
3	Painful erythema, edema, or ulcers, and cannot eat	Wait one week and if symptoms improve redose at 25% dose reduction
4	Requires parenteral or enteral support	Wait one week and if symptoms improve redose at 50% dose reduction

Patients with impaired hepatic function:
AIDS-KS Patients Experience with CAELYX® in treating AIDS-KS patients with hepatic impairment is limited. Therefore, based on experience with doxorubicin HCl, it is recommended that CAELYX® dosage be reduced if the bilirubin is elevated as follows: serum bilirubin 21 to 51 μmol/L (1.2-3.0 mg/dl), give 50% of normal dose; >51 μmol/L, give 25% of normal dose.

Breast Cancer/Ovarian Cancer Patients CAELYX® pharmacokinetics determined in a small number of ovarian cancer 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 program as follows:

- At initiation of therapy, if the bilirubin is between 21 to 51 μmol/L (1.2-3.0 mg/dl), the first dose is reduced by 25%.
- If the bilirubin is >51 μmol/L (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.

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 is not 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 who have had splenectomy, treatment with CAELYX® is not recommended.

Reconstitution:

Parenteral Products:

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

The appropriate dose of CAELYX®, up to a maximum of 90 mg, must be diluted in 250 mL of (5%) Dextrose Injection USP, prior to administration. For doses ≥90 mg, dilute CAELYX® in 500 mL of (5%) Dextrose USP Injection, prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in CAELYX®.

- Do not use with In-Line Filters.
- Do not mix with other drugs.
- Do not use with any diluent other than (5%) Dextrose Injection USP.
- Do not use any bacteriostatic agent, such as benzyl alcohol.

It is recommended that the CAELYX® infusion line be connected through the side port of an intravenous infusion of (50 mg/mL) (5%) Dextrose USP. Infusion may be given through a peripheral vein.

CAELYX® is not a clear solution but a translucent, red liposomal dispersion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Do not use material that shows evidence of precipitation or any other particulate matter. Discard unused portion.

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.

OVERDOSAGE

Acute overdosage with doxorubicin HCl causes increases in mucositis, leukopenia and thrombocytopenia.

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

Chronic overdosage with cumulative doses of doxorubicin HCl exceeding 550 mg/m^2 body surface, increases the risk of cardiomyopathy and resultant congestive heart failure. Doxorubicin HCl cardiomyopathy has been reported to be associated with a persistent reduction in the voltage of QRS wave, a prolongation of the systolic time interval and a reduction of the left ventricular ejection fraction (LVEF). Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. Reduction of afterload with vasodilating agents has been recommended.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

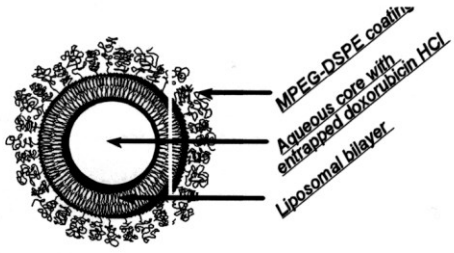
ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The active ingredient of CAELYX® (Pegylated Liposomal Doxorubicin Hydrochloride for Injection) is doxorubicin HCl. The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

CAELYX® is doxorubicin HCl encapsulated in long-circulating STEALTH® liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH® liposomes of CAELYX® are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

Representation of a STEALTH® liposome:



STEALTH® liposomes have a half-life of approximately 73.9 hours in humans. They are stable in blood, and direct measurement of liposomal doxorubicin shows that at least 90% of the drug (the assay used cannot quantify less than 5-10% free doxorubicin) remains liposome-encapsulated during circulation.

It is hypothesized that because of their small size (ca. 100 nm) and persistence in the circulation, the pegylated CAELYX® liposomes are able to penetrate the altered and often compromised vasculature of tumors. This hypothesis is supported by studies using colloidal gold-containing STEALTH® liposomes, which can be visualized microscopically. Evidence of penetration of STEALTH® liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C-26 colon carcinoma tumors. Once the STEALTH® liposomes distribute to the tissue compartment, the encapsulated doxorubicin HCl becomes available. The exact mechanism of release is not understood.

Pharmacokinetics

Population Pharmacokinetics

The pharmacokinetics of CAELYX® was evaluated in 120 patients from 10 different clinical trials using the population pharmacokinetic approach. The pharmacokinetics of CAELYX® over the dose range of 10 mg/m^2 to 60 mg/m^2 body surface, was best described by a two-compartment non-linear model with zero-order input and Michaelis-Menten elimination. The mean intrinsic clearance of CAELYX® was 0.030 L/h/m^2 (range 0.008 to 0.152 L/h/m^2) and the mean central volume of distribution was 1.93 L/m^2 (range 0.96 - 3.85 L/m^2) approximating the plasma volume. The apparent half-life ranged from 24 – 231 hours, with a mean of 73.9 hours. The apparent non-linearity suggests that the clearance of CAELYX® is saturable, and that greater than dose-proportional increases in exposure occur as the dose is increased.

Breast Cancer

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 0.0160 L/h/m^2 (range 0.0080 - 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

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

The plasma pharmacokinetics, and tumor localization of CAELYX® were studied in 42 patients with AIDS- related Kaposi's sarcoma (KS) who received single doses of 10 or 20 mg/m^2 body surface, administered by a 30-minute infusion. Twenty-three of these patients received single doses of both 10 and 20 mg/m^2 body surface, with a 3-week wash-out period between doses.

The pharmacokinetic parameter values of CAELYX® are presented in the following table:

Table 11 - Pharmacokinetic Parameters in CAELYX®-Treated Patients (Mean ± SD)		
	Dose	
Parameter (units)	**10 mg/m^2 body surface (n=23)**	**20 mg/m^2 body surface (n=23)**
Peak Plasma Concentration (μg/mL)	4.12 ± 0.215	8.34 ± 0.49
Plasma Clearance (L/h/m^2)	0.0556 ± 0.01	0.041 ± 0.004
Steady-State Volume of Distribution (L/m^2)	2.83 ± 0.145	2.72 ± 0.120
AUC (μg/mL•h)	277 ± 32.9	590 ± 58.7
First Phase (λ_1) Half-Life (h)	4.7 ± 1.1	5.2 ± 1.4
Second Phase (λ_2) Half-Life (h)	52.3 ± 5.6	55.0 ± 4.8

Across this dosage range, CAELYX® displayed linear pharmacokinetics. Disposition occurred in two phases after CAELYX® administration, with a relatively short first phase (~5 hours) and a prolonged second phase (~55 hours) that accounted for the majority of the area under the curve (AUC).

In contrast to the pharmacokinetics of doxorubicin, which displays a large volume of distribution, the steady-state volume of distribution of CAELYX® indicated that CAELYX® was confined mostly to the vascular fluid volume. Plasma protein binding of CAELYX® has not been determined; however, the plasma protein binding of doxorubicin is approximately 70%.

Doxorubicinol, the major metabolite of doxorubicin, was detected at very low levels (range: 0.8 to 26.2 ng/mL) in the plasma of patients who received 10 or 20 mg/m^2 (body surface) of CAELYX®. The plasma clearance of CAELYX® was slow, with a mean clearance value of 0.042 L/h/m^2 at a dose of 20 mg/m^2 body surface.

Kaposi's sarcoma lesions and normal skin biopsies were obtained at 48 and 96 hours post infusion of 10 or 20 mg/m^2 (body surface) of CAELYX® in 22 patients. Significantly higher doxorubicin concentrations were found in KS lesions than in normal skin biopsies at both sampling times and dose levels. The median doxorubicin concentrations ranged from 2-fold to 20-fold higher in KS lesions than in normal skin.

Tissue Distribution

The concentration of CAELYX® in AIDS-KS lesions was a median of 21 times higher than in normal skin at 48 hours post-treatment. Population pharmacokinetic analyses suggested that there were small differences in the volume of distribution between tumor types, with the largest volume of distribution in patients with AIDS-KS (2.24 L/m^2), and the smallest volume of distribution in patients with breast carcinoma (1.12 L/m^2). The volume of distribution in the ovarian carcinoma population is 1.56 L/m^2.

Pharmacokinetics of CAELYX® in Elderly Patients
The population-based pharmacokinetic analysis included patients from 21 to 73 years of age. The results of this analysis suggested that age did not influence the pharmacokinetic profile of CAELYX®.

Pharmacokinetics of CAELYX® in 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.

Pharmacokinetics of CAELYX® in Patients with Hepatic Insufficiency
Based upon population pharmacokinetics, bilirubin concentrations did not affect the pharmacokinetics of CAELYX®. It should be noted however, that few patients with elevated bilirubin were included in the analysis and that the highest bilirubin in the study was 4.0 mg/dL. Until more data are available demonstrating the safety of CAELYX® in this patient population, suggested dosing reductions mentioned under **DOSAGE AND ADMINISTRATION** should be followed.

STORAGE AND STABILITY

- CAELYX® should not be used after the expiry date stated on the label and carton.

- Unopened vials of CAELYX® should be stored at 2°C- 8°C. Avoid freezing.

- After dilution:
    - Chemical and physical in-use stability has been demonstrated for 24 hours at 2ºC to 8ºC.
    - From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2ºC to 8ºC.
    - Partially used vials must be discarded.

- CAELYX® should not be used if it shows evidence of precipitation or any other particulate matter.

- CAELYX® should not be used if it shows a discoloration of the solution.

- Keep out of reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CAELYX® (Pegylated Liposomal Doxorubicin Hydrochloride for Injection) is provided as a sterile, translucent, red liposomal dispersion in 10 mL glass, single-use vials. Vials contain 20

mg doxorubicin HCl in a pegylated liposomal formulation at a concentration of 2 mg/mL in water for injection and a pH of 6.0 - 7.0.

The STEALTH® liposome carriers are composed of N-(carbamoyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains approximately 2 mg of ammonium sulfate; 1.55 mg of histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control and 94 mg of sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the STEALTH® liposomes.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

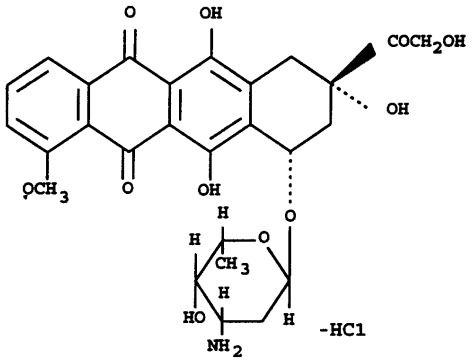
Proper name: Doxorubicin Hydrochloride

Chemical name: (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride

Molecular formula: $C_{27}H_{29}NO_{11}$•HCl

Molecular mass: 579.99

Structural formula:



Physicochemical properties: Doxorubicin is a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius* var. *caesius*. It is a red-orange, odorless, crystalline powder, m.p. 204ºC - 205ºC, pH (conc. 5 mg/mL) 4.0 - 5.5, pKa 8.22, $[\alpha]^{20}_{D}$ +268º- 270º (conc. 0.1% methanol), soluble in water and alcohols.

CLINICAL TRIALS

Breast Cancer

A phase III randomized, controlled parallel-group, open-label, multicentre study of CAELYX® 50 mg/m^2 q 4 weeks vs, doxorubicin hydrochloride 60 mg/m^2 q 3 weeks in patients with metastatic breast cancer was completed in 509 patients.

The protocol-specified primary 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. Median PFS for CAELYX® was 6.9 months and for doxorubicin 7.8 months, not statistically significant.

Table 12 - Progression-Free Survival in Breast Cancer Patients

Protocol No. I97-328

		Number of Subjects					
	n	**Censored**	**Progressed[a]**	**Median PFS**	***P*-value[b]**	**HR**	**95% CI for HR[c]**
CAELYX®	254	52	202	6.9 months	0.99	1.00	0.82-1.22
Doxorubicin	255	47	208	7.8 months			

a: Deaths within 4 months of last tumor evaluation indicating no progression are considered events.
b: Stratified log rank test to test superiority of CAELYX® to doxorubicin.
c: Adjusted for the interim analysis (95.01% CI provided).

Figure #1: Kaplan-Meier Curve for Progression-free Survival in Breast Cancer Patients

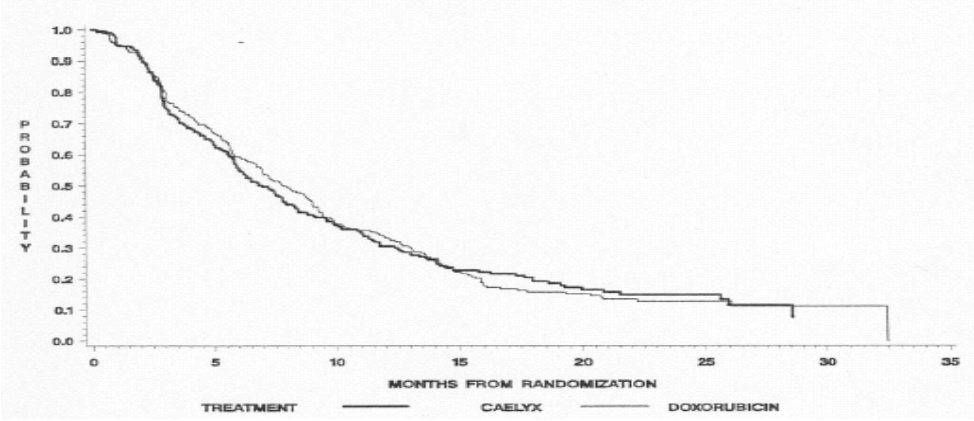


Table 13 - Overall Survival in Breast Cancer Patients							
	n	**Censored**	**Dead**	**Median OS**	***P*-value[a]**	**HR**	**95% CI for HR[b]**
CAELYX® Doxorubicin	254 255	110 113	144 142	21 months 22 months	0.59	0.9	0.74-1.19
a: Stratified log rank test to test superiority of CAELYX® to doxorubicin b: Adjusted for the interim analysis (95.01% CI provided)							

Figure #2: Kaplan-Meier Curve for Overall Survival in Breast Cancer Patients

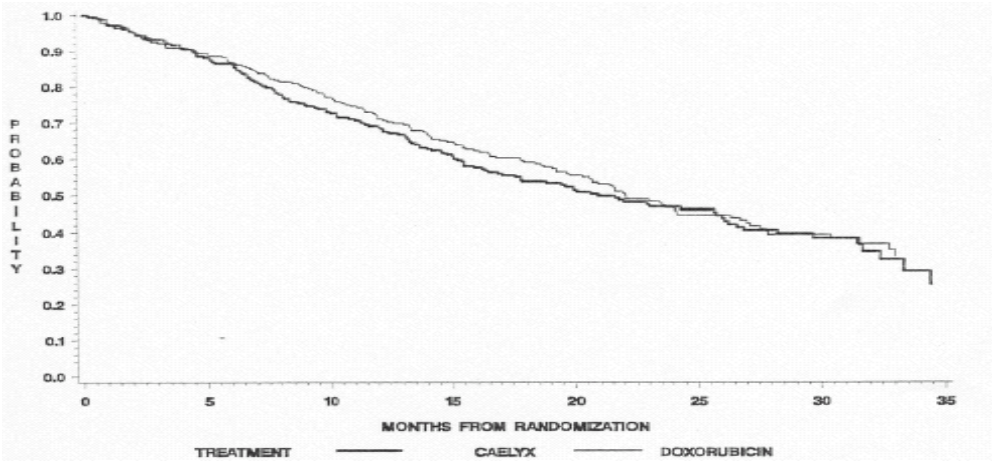


Table 14 - Objective Response to Treatment in Breast Cancer Patients		
	Number (%) of Subjects[a]	
	CAELYX® (n=209)	**Doxorubicin (n=201)**
Overall Response (CR+ PR)	68 (33)	77 (38)
Complete Response (CR)	7 (3)	9 (4)
Partial Response (PR)	61 (29)	68 (34)
Stable Disease (SD)	52 (25)	51 (25)
Progressive Disease (PD)	37 (18)	22 (11)
No assessment	52 (25)	51 (25)
a: Based on the number of subjects with measurable disease.		

In the breast cancer pivotal phase III trial comparing CAELYX® (50 mg/m^2 every 4 weeks) to doxorubicin (60 mg/m^2 every 3 weeks), 10/254 patients randomized to receive CAELYX® versus 48/255 patients randomized to receive doxorubicin met the protocol-defined criteria for cardiotoxicity during treatment and/or follow-up. Cardiotoxicity was defined as a decrease of 20 percentage points or greater from baseline if the resting LVEF remained in the normal range or a decrease of 10 percentage points or greater if the LVEF became abnormal (less than the lower limit for normal). The risk of developing a cardiac event as a function of cumulative anthracycline dose was significantly lower with CAELYX® than with doxorubicin (HR [doxorubicin/CAELYX®] = 3.16, P<0.001). At cumulative doses greater than 450 mg/m^2 there were no cardiac events with CAELYX®. Patients were also assessed for signs and symptoms of congestive heart failure (CHF). None of the 10 CAELYX® patients, who had cardiotoxicity by LVEF criteria, developed signs and symptoms of CHF. In contrast, 10 of 48 doxorubicin patients, who had cardiotoxicity by LVEF criteria, developed signs and symptoms of CHF.

Table 15 - Cardiac Toxicity During Treatment and Follow-Up in Breast Cancer Patients

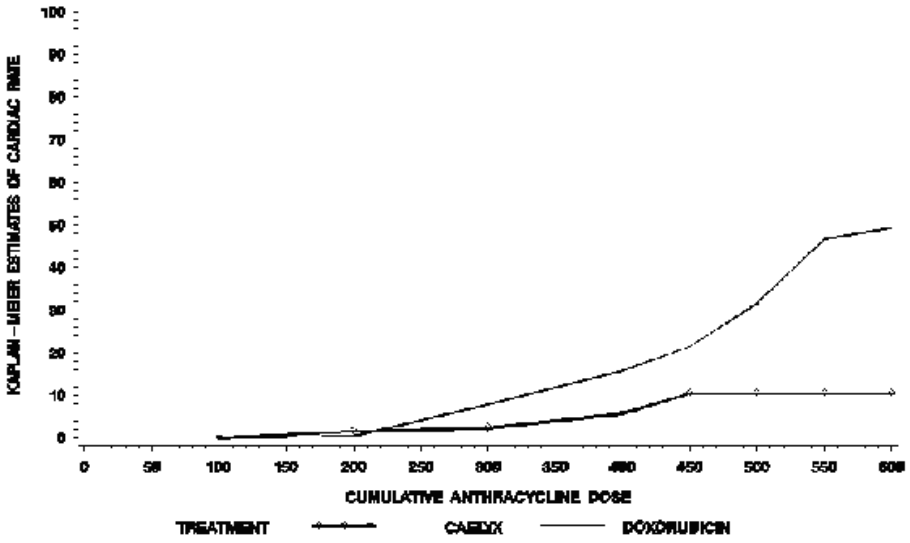
Protocol No. I97-328

	Number of Subjects	
	CAELYX® (n=254)	**Doxorubicin (n=255)**
Subjects developed cardiotoxicity (LVEF defined)	10	48
Cardiotoxicity (with signs & symptoms of CHF)	0	10
Cardiotoxicity (no signs & symptoms of CHF)	10	38

Table 16 - Cumulative Anthracycline Dose and Cardiotoxicity in Breast Cancer Patients Subgroups

	Number of Subjects				
	n	**Censored**	**Cardiotoxicity Events**	**HR**	**95% CI for HR**
≥55 years old CAELYX® Doxorubicin	 159 152	 153 134	 6 18	2.04	0.81-5.18
Prior Adjuvant Anthracycline CAELYX® Doxorubicin	 38 40	 37 29	 1 11	7.27	0.93-56.80
Cardiac Risk Factor CAELYX® Doxorubicin	 122 121	 117 100	 5 21	2.7	1.01-7.18

Figure #3: Kaplan-Meier Curve for Rate of Cardiotoxicity vs. Cumulative Anthracycline Dose in Breast Cancer Patients



In 418 patients with solid tumors (including a subset of patients with breast and ovarian cancers) treated with CAELYX® at a dose of 50 mg/m^2/cycle, the incidence of clinically significant cardiac dysfunction was low. Only 13 of 88 patients (15%) with cumulative anthracycline dose >400 mg/m^2 body surface, had a clinically significant change in their LVEF (defined as LVEF <45% or a decrease of at least 20 percentage points from baseline).

In addition, endomyocardial biopsies were performed in 8 solid tumor patients with cumulative anthracycline dose of 509 mg/m^2-1,680 mg/m^2 body surface. The range of Billingham cardiotoxicity scores was grades 0-1.5. These grading scores are consistent with no or mild cardiotoxicity.

Table 17 - Most Common Treatment Related (≥5%) Adverse Events in Breast Cancer Patients						
	Number (%) of Subjects					
	CAELYX® (n=254)			Doxorubicin (n=255)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
PPE	123 (48)	42 (17)	0	5 (2)	0	0
Nausea	94 (37)	8 (3)	0	136 (53)	12 (5)	0
Mucositis	59 (23)	10 (4)	0	33 (13)	5 (2)	0
Stomatitis	55 (22)	12 (5)	0	38 (15)	4 (2)	0
Alopecia	51 (20)	0	0	169 (66)	0	0
Vomiting	48 (19)	2 (<1)	0	78 (31)	11 (4)	0
Fatigue	31 (12)	2 (<1)	0	40 (16)	4 (2)	0
Anorexia	27 (11)	3 (1)	0	26 (10)	1(<1)	0
Asthenia	26 (10)	3 (1)	0	32 (13)	3 (1)	0
Rash	25 (10)	6 (2)	0	4 (2)	0	0
Abdominal Pain	21 (8)	3 (1)	0	11 (4)	3 (1)	0
Constipation	21 (8)	2 (<1)	0	24 (9)	1 (<1)	0
Pigmentation Abnormal	21 (8)	1 (<1)	0	6 (2)	1 (<1)	0
Fever	20 (8)	0	0	18 (7)	2 (<1)	1 (<1)
Diarrhea	18 (7)	3 (1)	0	20 (8)	2 (<1)	0
Erythema	18 (7)	2 (<1)	0	3 (1)	0	0
Weakness	14 (6)	1 (<1)	0	20 (8)	4 (2)	0
Mouth Ulceration	13 (5)	1 (<1)	0	9 (4)	0	0
Anemia	12 (5)	2 (<1)	1(<1)	19 (7)	3 (1)	1(<1)
Neutropenia	10 (4)	3(1)	1 (<1)	25 (10)	10 (4)	9 (4)

Ovarian Cancer

Pivotal Phase III Study

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. All patients entered into this study had failed a first-line platinum-containing regimen, usually a combination of platinum and paclitaxel, either used in combination or in sequence. A small number of patients had received prior therapy with platinum alone.

Pivotal Phase III Study - Efficacy

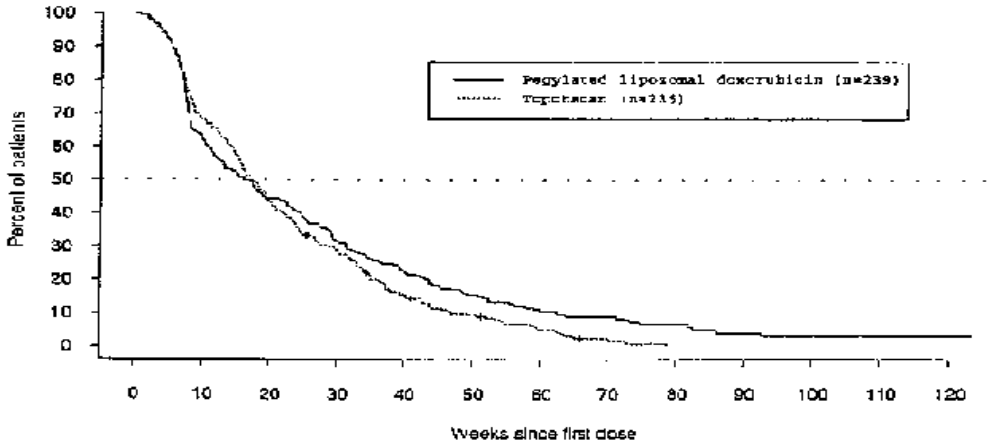
For the protocol-specified primary endpoint of time to progression for the 416 (207 CAELYX®, 209 topotecan) evaluable patients (patients who were randomized, met enrolment criteria, and received at least 2 cycles of study drug), the results of the study demonstrate therapeutic equivalency of CAELYX® vs. topotecan. The median time to progression for evaluable patients was 148 days for CAELYX® and 134 days for topotecan with a hazard ratio of 1.262, 90% CI 1.062-1.500, *P*=0.026.

The time to progression for the Intent to Treat (ITT) population n=474 (239 CAELYX®, 235 topotecan; patients who were randomized and received at least a partial dose of study drug) favored CAELYX® over topotecan with a hazard ratio of 1.176, 90% CI 1.002-1.381, *P*=0.095. The median time to progression was 113 days for CAELYX® and 119 days for topotecan.

Table 18 - Objective Response, Overall Response and Stratified by Platinum Sensitivity (ITT Ovarian Cancer Population)

	CAELYX® (n=239)	Topotecan (n=235)
Overall Response		
n	239	235
Total	47 (19.7%)	40 (17%)
Complete	9 (3.8%)	11 (4.7%)
Partial	38 (15.9%)	29 (12.3%)
Platinum-Refractory		
n	130	124
Total	16 (12.3%)	8 (6.5%)
Complete	1 (0.8%)	1 (0.8%)
Partial	15 (11.5%)	7 (5.6%)
Platinum-Sensitive		
n	109	111
Total	31 (28.4%)	32 (28.8%)
Complete	8 (7.3%)	10 (9.0%)
Partial	23 (21.1%)	22 (19.8%)

Figure #4 - Kaplan-Meier Curve of Progression-free Survival (Intent-to-treat Ovarian Cancer Population)[15]

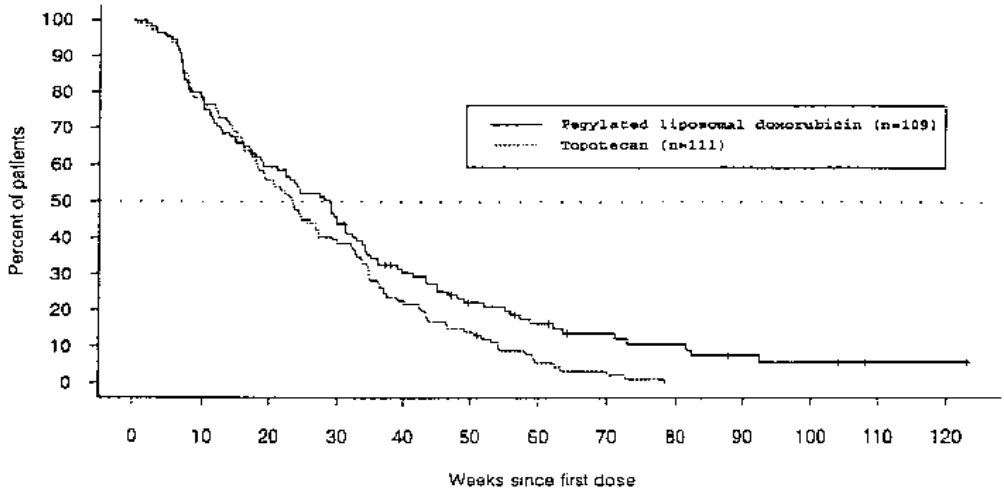


For the entire ITT population, overall survival for CAELYX® was at least equivalent to topotecan with ratio of 1.121 (90% CI 0.920-1.367, *P*=0.34) in favor of CAELYX®.

In the protocol-defined ITT population platinum-sensitive subgroup (patients who responded to initial platinum-based therapy and had a progression-free interval of greater than 6 months off treatment), both time to progression and overall survival were significantly in favor of CAELYX® (Table 19).

Table 19 - Pivotal Phase III Study Protocol 30-49 (Ovarian Cancer Patients)				
Time to Progression for Platinum-Sensitive Subgroup of ITT population				
Treatment	**n**	**Median (days)**	**Hazard Ratio (HR)**	**90% CI for HR**
CAELYX®	109	202	1.349	1.065 - 1.709
Topotecan	111	163		
Overall Survival for Platinum-Sensitive Subgroup of ITT population				
CAELYX®	109	756	1.72	1.222 - 2.422
Topotecan	111	498		

Figure #5 - Kaplan-Meier Curve of Progression-free Survival (Intent-to-treat Population; Platinum-Sensitive Ovarian Cancer Patients).[15]



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

Pivotal Phase III Study - Safety

Overall, treatment-related adverse events observed with CAELYX® tended to be of mild or moderate severity.

The most common drug-related adverse events associated with CAELYX® were PPE (Palmar-Plantar Erythrodysesthesia) and stomatitis and were severe in 23% and 8% of CAELYX®-treated patients respectively. Both were easily managed with dose reduction or delays and were seldom treatment-limiting or life-threatening.

The most common drug-related adverse events associated with topotecan were hematologic toxicities (neutropenia, anemia, thrombocytopenia, leukopenia), nausea and alopecia. Hematologic events, nausea, and alopecia were less frequent and less severe with CAELYX®

compared with topotecan. Hematologic toxicity with topotecan was frequently associated with clinical sequelae, such as infection, or the need for transfusions or hematopoietic growth factors.

Table 20 - Most Frequently Reported Treatment-Related Adverse Events for Each Ovarian Cancer Treatment Group - Phase III Study

	CAELYX® (n=239)		Topotecan (n=235)	
	All Severities	Grade III/IV Severity	All Severities	Grade III/IV Severity
Neutropenia	84 (35%)	29 (12%)	191 (81%)	178 (76%)
Anemia	85 (36%)	13 (5%)	169 (72%)	66 (28%)
Thrombocytopenia	31 (13%)	3 (1%)	152 (65%)	80 (34%)
Leukopenia	87 (36%)	24 (10%)	149 (63%)	117 (50%)
Alopecia	38 (16%)	3 (1%)	115 (49%)	14 (6%)
PPE*	117 (49%)	55 (23%)	2 (1%)	0
Stomatitis	95 (40%)	20 (8%)	35 (15%)	1 (0.4%)
Nausea	85 (36%)	7 (3%)	127 (54%)	14 (6%)

* PPE = Palmar-plantar erythrodysesthesia

There was no evidence of a relationship between cumulative CAELYX® dose and change from baseline for LVEF (Left Ventricular Ejection Fraction).

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.

AIDS-KS

Efficacy data on refractory patient population

CAELYX® was studied in an open-label, single-arm, multicenter study utilizing CAELYX® at 20 mg/m^2 by intravenous infusion every three weeks generally until progression or intolerance occurred. In an interim analysis, the treatment history of 383 patients was reviewed, and a cohort of 77 patients was retrospectively identified as having disease progression on prior systemic combination chemotherapy (at least 2 cycles of a regimen containing at least two of three treatments: bleomycin, vincristine or vinblastine, or doxorubicin) or as being intolerant to such therapy. Of the 77 patients selected, 66 had disease progression on conventional chemotherapy prior to entering the trial and 11 could not continue systemic chemotherapy because of intolerable toxicity. These 77 patients were predominantly white, homosexual males with a mean age of 38 years.

Two analyses of tumor response were used to evaluate the effectiveness of CAELYX®:

1- Indicator Lesion Assessment: A retrospective analysis was conducted based on analysis of five indicator lesions. A partial response was defined as a decrease of ≥50% in the total size of the indicator lesions compared to study entry, or a decrease of 50% in the number of raised lesions.

2- Investigator Assessment: Investigator assessment of response was based on ACTG criteria. Partial response was defined as no new lesions, sites of disease, or worsening edema. In addition, one of the following criteria had to be fulfilled: (1) a 50% or greater

decrease in the number of all previously existing lesions; (2) a complete flattening of at least 50% of all previously raised lesions; (3) a 50% decrease in the sum of the products of the largest perpendicular diameters of the indicator lesions; or (4) the patient met the criteria for Clinical Complete Response except the patient had residual tumor-associated edema or effusion.

Analyses of efficacy were conducted using both conventional ("best") and "conservative" response methodologies for the 77 refractory patients. According to the "conservative" response methodology (updated ACTG response criteria), patients had to meet the response criteria at a minimum of two consecutive clinical evaluations, separated by a minimum of 21 days, with no record of prior disease progression. The results obtained using both of these methodologies are summarized below:

Table 21 - Best Response in Refractory[a] AIDS-KS

	Indicator Lesion Assessment	**Investigator Assessment**
Number of Patients	**77**	**77**
Best Response		
Complete	0	1 (1.3%)
Partial	52 (67.5%)	43 (55.8%)
Stable	20 (26.0%)	29 (37.7%)
Progression	5 (6.5%)	4 (5.2%)
Time to PR and/or CR (days)		
Median	69	94
Range	1-351	1-280
Duration of PR and/or CR (days)		
Median	64	113
Range	1-211	15-368

[a] Patients with disease that progressed on prior combination chemotherapy or who were intolerant to such therapy.
PR = Partial response; CR = Complete response

Table 22 - Best "Conservative" Response in Refractory[a] AIDS-KS		
	Indicator Lesion Assessment	**Investigator Assessment**
Number of Patients	**77**	**77**
Best Response		
Complete	0	1 (1.3%)
Partial	26 (33.8%)	33 (42.9%)
Stable	19 (24.7%)	22 (28.6%)
Progression	32 (41.6%)	21 (27.3%)
Time to PR and/or CR (days)		
Median	92	99
Range	1-414	1-304
Duration of PR and/or CR (days)		
Median	65	113
Range	22-211	21-368

[a] Patients with disease that progressed on prior combination chemotherapy or who were intolerant to such therapy.
PR = Partial response; CR = Complete response

Controlled trials

Two phase III, randomized, multicenter trials have been performed, comparing CAELYX® at a dose of 20 mg/m^2 with a combination chemotherapy regimen of 20 mg/m^2 Adriamycin®, 10 U/m^2 bleomycin and 1.0 mg vincristine (ABV) or 15 U/m^2 bleomycin and 1.4 mg/m^2 vincristine (BV) in the treatment of severe AIDS-KS. Patients received up to 6 cycles of either treatment regimen every 2 weeks (ABV-controlled) or 3 weeks (BV-controlled). Patients with extensive and progressive cutaneous KS lesions or mucocutaneous disease and/or documented visceral disease were enrolled in these studies. Most patients had between 10-50 lesions at baseline and CD4 counts of less than 50 cells per mm^3 A total of 499 patients were treated in these two studies: 254 with CAELYX®, 125 with ABV, and 120 with BV.

The primary efficacy parameter used in studies 30-10 and 30-11 was overall clinical assessment as determined by the investigator. Tumor response was to be classified as complete, clinically complete, partial, stable disease, or progressive disease, based on a refinement of the ACTG criteria published in 1989. In order to be classified as a "responder" (partial response (PR), clinical complete response (CCR), or complete response (CR)), the patient must have had at least two sequential investigator assessments, at least 28 days apart, that consistently confirmed the response. Partial response was defined as above (see efficacy data on refractory patient population; definition of investigator assessment). In conjunction with investigator assessment, additional assessments were also made, among which, assessment of indicator lesion characteristics and quality of life (QOL) questionnaires. Primary efficacy results are summarized below:

Table 23 - Controlled Trials - Response Summary			
	CAELYX®	**ABV**	**BV**
	(N = 254)	**(N = 125)**	**(N = 120)**
Complete/Partial Response	132 (52.0%)	31 (24.8 %)	28 (23.3%)
Time to CR/PR - Median (Days)	43	50	64
Duration - Median (Days)	119	92	123

CR = Complete response; PR = Partial response

As evaluated by investigator assessment, the overall (complete/partial) response rate for CAELYX® was significantly (P<0.001) superior to that of ABV and BV. In the CAELYX® group, 8 patients (3.1%) achieved a clinical complete response and 124 patients (48.8%) achieved a partial response. In the ABV group, no patients achieved a clinical complete response and 31 (24.8%) achieved a partial response; in the BV group, 1 patient (0.8%) achieved a clinical complete response and 27 (22.5%) achieved a partial response.

Response in both the CAELYX® patients and the control arms was associated with significant improvements in the characteristics of the KS lesions, including a reduction in lesion thickness and nodularity, improvement in lesion color, and resolution of lesion-associated edema. CAELYX® patients also showed a mean decrease of indicator lesion size by 26.0% by the end of treatment. ABV patients showed a mean decrease of 14.6%, whereas BV patients showed a slight increase (0.2%). Compared to ABV and BV treatment, the response rates achieved by CAELYX® also translated into improved QOL for patients.

Cardiotoxicity

An increased incidence of congestive heart failure is associated with doxorubicin therapy at cumulative lifetime doses >450 mg/m^2 body surface, or at lower doses for patients with cardiac risk factors. Endomyocardial biopsies on ten AIDS-KS patients receiving cumulative doses of CAELYX® greater than 460 mg/m^2 body surface, indicate no evidence of anthracycline-induced cardiomyopathy in 5 patients, minimal myocardial cell damage (<5%) in 4 patients and in 1 patient cell damage was >6-15%. The recommended dose of CAELYX® for AIDS-KS patients is 20 mg/m^2 body surface, every two-to-three week. The cumulative dose at which cardiotoxicity would become a concern for these AIDS-KS patients (>400 mg/m^2 body surface) would require more than 20 courses of CAELYX® therapy over 40 to 60 weeks.

DETAILED PHARMACOLOGY

ANIMAL PHARMACOLOGY

Therapeutic Efficacy of CAELYX®

The efficacy of CAELYX®, equivalent doses of conventionally formulated doxorubicin hydrochloride and doxorubicin hydrochloride encapsulated in conventional liposomes have been compared in a variety of murine tumor models including several human xenograft models. In every model examined, CAELYX® was more effective than the same dose of doxorubicin hydrochloride in inhibiting or halting tumor growth, in effecting cures and/or in prolonging the survival of tumor-bearing animals; and in no case was CAELYX® less effective than doxorubicin hydrochloride. CAELYX® was more active in both solid and dispersed tumors and was more effective than doxorubicin hydrochloride in preventing spontaneous metastases from intramammary implants of two different mammary tumors in mice. In two tumor models in

which they were compared, CAELYX® was also more effective than the same dose of doxorubicin hydrochloride encapsulated in non-pegylated liposomes, demonstrating the impact of the long-circulating liposome.

Pharmacokinetics
Single dose studies were performed in rats and dogs, and multiple dose pharmacokinetic studies were also conducted in rats, rabbits and dogs to characterize the plasma pharmacokinetics of CAELYX®.

The plasma pharmacokinetics of CAELYX® and doxorubicin were found to be significantly different in all species evaluated. The plasma concentration of doxorubicin was up to 2000-fold higher in CAELYX®-treated animals after intravenous injection of equivalent doses of CAELYX® and doxorubicin hydrochloride. Plasma concentration by time data were best fit with a bi-exponential curve, with a relatively short first phase (half-life = 1 to 3 hours), and a more prolonged second phase, which represented the majority of the AUC (area-under- the-curve), and a half-life ranging from 20 to 30 hours. The volume of distribution was smaller, and clearance was substantially decreased when compared to doxorubicin hydrochloride. Although plasma concentration and AUC were dose-dependent, CAELYX® disposition kinetics were independent of dose. No evidence of drug accumulation was seen in dogs treated with up to 1.0 mg/kg of CAELYX® every three weeks. The plasma pharmacokinetics of CAELYX® in rats did not change with repeated dosing.

Despite the higher plasma concentration of doxorubicin after CAELYX® treatment, the stability of the STEALTH® liposome and its low rate of doxorubicin release (leakage) in plasma results in very low levels of free (non-liposomal) doxorubicin hydrochloride in the bloodstream. Virtually the entire CAELYX® dose administered to animals can be accounted for in the plasma in 2-5 minutes after treatment, suggesting that no sudden burst of drug release occurs after drug injection, as has been reported for conventional, non-STEALTH® liposomal formulations of doxorubicin hydrochloride. Direct measurements of the amount of liposomal drug in the plasma shows that more than 90% to 95% of the doxorubicin, remains encapsulated in liposomes.

Tissue levels of doxorubicin were determined in tumor-bearing mice and in non-tumor-bearing rats and dogs. In the tumor model studies, tumor AUC's in CAELYX®-treated animals ranged from 7-fold higher in a murine C26 colon carcinoma model to 25-fold greater in the human prostatic xenograft than in mice treated with the same dose of doxorubicin hydrochloride. Tumor and normal tissue levels of doxorubicin continued to rise for at least 24 hours in CAELYX®-treated mice but peaked after 1-4 hours in animals that received doxorubicin hydrochloride, declining rapidly thereafter.

Doxorubicin concentrations persisted in the tissues in CAELYX®-treated animals, owing to the slower clearance of liposome-associated drug, resulting in significantly higher tissue AUC's. It is known that doxorubicin-associated toxicity, particularly cardiotoxicity, is associated with the high peak concentrations of doxorubicin, but not with AUC. Treatment regimens that minimize peak doxorubicin plasma concentrations, but maintain cumulative AUC, are associated with reduced risk of cardiomyopathy and do not compromise anti-tumor activity. The reduced cardiac tissue concentrations in CAELYX®-treated animals correlate well with the observation that CAELYX® is less cardiotoxic than doxorubicin hydrochloride in animals (see **TOXICOLOGY**, Special **Studies**, **Cardiotoxicity**).

The higher AUC's in the tissues also did not correlate with increased toxicity, with the exception of cutaneous lesions. Doxorubicin concentrations were higher at sites of cutaneous lesions than in normal skin, with levels falling rapidly after treatment stopped and nearing the concentrations found in normal skin by the end of the recovery period. It could not be determined if lesions formed because of increased doxorubicin concentrations, or whether doxorubicin concentration was secondarily increased as a result of extravasation of CAELYX® at pre-existing sites of tissue damage. Studies in dogs have demonstrated that the incidence and severity of the cutaneous lesions is related to dose intensity, with lower dose levels associated with decreased lesion formation (see **TOXICOLOGY, Special Studies, Dermal Lesion Development**).

TOXICOLOGY

Acute Toxicity

In single dose studies, the acute toxicity of CAELYX® was similar for mice, rats, and dogs. In the rat, the incidence and severity of clinical observations were dose-related and included tail and footpad lesions, swelling and inflammation of the penis and scrotum, rough haircoat, alopecia, hypoactivity, hunched posture, respiratory distress, and reduced body weight gain. Reversible myelotoxicity was noted based on decreased RBC, WBC, hemoglobin, and hematocrit. Increases occurred in BUN and cholesterol levels.

Dogs were the most sensitive species. Treatment-related toxicity included dermal toxicity, reversible myelotoxicity, hematologic changes, increased BUN, gastrointestinal toxicity, body weight loss, reversible cutaneous lesions, and alopecia. Myelotoxicity was less severe compared with the doxorubicin hydrochloride group.

In a single dose study, MPEG-DSPE micelles, a component of the CAELYX® liposome formulation, had no acute toxic effects in mice when administered at a lipid dose approximately 30-fold that found in the dose of 20 mg/m^2 recommended for humans.

Long-term Toxicity

The toxicity of CAELYX® following repeated administration was similar in rats and dogs and an extension of the findings in the acute studies. Treatment-related effects included dermatologic toxicity, body weight and food consumption changes, alopecia, myelotoxicity (bone marrow cellularity changes), and hematologic effects (leukopenia and lower erythron mass). Dogs also showed gastrointestinal toxicity and no pathologic signs of toxicity. In the long-term studies, CAELYX® was compared with non-liposomal doxorubicin hydrochloride:

Table 24 - Comparative Long-term Toxicity Studies				
Species	**No./ Sex**	**No. of Doses**	**Dose (mg/kg)**	**CONCLUSIONS**
Rat	Groups of 30 15 Female 15 Male	13 dose q3d	CAELYX® 0.25, 1.0, 1.5 Dox HCl 1	• Dosing halted in 1.5 mg/kg CAELYX® group due to effect of dermal lesions on general health. Death of 1/10 males related to this toxicity. • CAELYX® induced dermal lesions at ≥1 mg/kg; readily reversible upon cessation of treatment. • CAELYX® less cardiotoxic, haemotoxic and nephrotoxic than equivalent dose of doxorubicin hydrochloride. • Other adverse effects similar in nature, incidence and severity in CAELYX® and doxorubicin hydrochloride groups. • No effect of placebo liposomes.
Dog	Groups of 6 Male	4 dose q7d	CAELYX® 1 Dox-HCl 1	• 1 CAELYX® and 1 Dox-HCl animal died during treatment. • Myelotoxicity milder in CAELYX® groups, with later onset, less severe changes and quicker recovery. • CAELYX® induced adverse inflammatory lesions of feet and legs; readily reversed upon cessation of treatment. • Other adverse effects comparable in CAELYX® and Dox-HCl treatment. • Dogs given placebo liposomes exhibited transient hypoactivity, flushing, emesis, prostration during 2nd dose. Reduced in incidence and severity at 3rd and 4th doses.
Dog	Groups of 6 Female 6 Male	10 dose q21d	CAELYX® 0.25, 0.75, 1.0 Dox-HCl 1.0	• Mild to moderate cardiomyopathy in all dogs treated with non-liposomal doxorubicin hydrochloride that worsened during the recovery period. • No evidence of cardiotoxicity in any CAELYX®-treated dog at interim or final necropsy. • Bone marrow hypocellularity in ribs and femur of doxorubicin hydrochloride-treated animals, with mild decreases in WBC count. Both resolved in 4-week recovery period. WBC depression only in CAELYX® groups, also resolved in recovery period • Alopecia and mild dermal ulcers seen in 0.75 and 1.0 mg/kg CAELYX® groups. Ulcers healed, but alopecia only partially resolved during recovery. • Placebo liposome effect (hypoactivity, emesis, etc.) could be controlled by reducing dose rate from 2.0 to 0.5 mL/min.

Carcinogenicity and Mutagenicity

Doxorubicin, the active component of CAELYX®, is both mutagenic and carcinogenic so conducting carcinogenicity and mutagenicity studies was not deemed necessary. Four studies were carried out with STEALTH® placebo liposome to confirm their lack of mutagenicity and genotoxicity.

Negative results were obtained in the Ames, the L5178Y mouse lymphoma, and chromosomal aberration assays *in vitro*, and the mouse bone marrow micronucleus assay *in vivo*.

Nephrotoxicity
Cynomolgus monkeys (3/sex) were administered a single intravenous dose of CAELYX® (Doxil® formulation) of 10 mg/kg (120 mg/m²; approximately two times the clinical dose) and followed for 28 days as a comparator arm in an acute toxicity study with an investigational doxorubicin formulation. Three male and 1 female monkeys were sacrificed on Day 11 or 15 in poor condition attributable to renal toxicity. Renal toxicity reflected in increased serum creatinine and blood urea nitrogen levels included tubular and/or glomerular changes and presented as renal hemorrhage and/or edema (cortex, pelvis or papilla), distal tubular dilatation, tubular protein casts, hypertrophy of the Bowman's capsular epithelial cells, interstitial neutrophil infiltration, and/or necrosis of renal adipose tissue. Renal toxicity has been observed with even lower single doses of doxorubicin HCl in rats and rabbits. However, 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.

Reproduction and Teratology
The potential developmental toxicity of CAELYX® was evaluated in rats and rabbits. In the first study, intravenous bolus injections of CAELYX® 0.1, 0.5, or 1.0 mg/kg was administered on gestation days 6, 9, 12, and 15; or STEALTH® placebo liposomes or saline on the same treatment schedule. An additional group received doxorubicin 0.2 or 0.4 mg/kg daily between gestation days 6 and 15. Equivalent maternal toxicity occurred in the CAELYX® 0.5 and 1.0 mg/kg groups and in the doxorubicin groups. CAELYX® 1.0 mg/kg induced decreased fetal weights, increases in fetal resorptions, and retarded ossification of caudal vertebrae and xiphoid centers in the fetuses. No adverse effects were seen in dams or fetuses in the placebo liposome or CAELYX® 0.1 mg/kg groups.

The embryotoxicity of CAELYX® was confirmed in the study in pregnant New Zealand White rabbits administered intravenous injections of CAELYX® 0.5, 1.5, or 2.5 mg/kg on gestation days 6, 9, 12, 15, and 18. All doses were maternally toxic. Four females that died (3 and 1 in the high- and mid-dose groups, respectively), surviving females in the mid- and high-dose groups (4 and 2, respectively), and 4 females (low-dose group) who aborted prior to the end of the study all had 100% resorbed conceptuses. The uterine of another female (low-dose group) who aborted prior to the end of the study consisted of 3 normal conceptuses, 4 late resorptions, and 5 early resorptions. CAELYX® is both embryotoxic and an abortifacient in rabbits.

Special Studies
Local Tolerance
Two single dose studies were conducted to examine the potential of CAELYX® to cause injury if accidentally extravasated. Rabbits received single intravenous or subcutaneous injections of 0.1 or 1.0 mL of undiluted CAELYX® 2.0 mg/mL, doxorubicin hydrochloride 2.0 mg/mL, or STEALTH® placebo liposomes. Histopathological evaluation of the intravenous injection sites revealed that CAELYX®, doxorubicin hydrochloride, and placebo liposomes were well tolerated with no gross or microscopic evidence of irritation.

In contrast, histopathological evaluation of the subcutaneous injection sites showed reversible mild to moderate dose-related inflammation at CAELYX® injections sites compared to moderate to severe inflammation and necrosis at doxorubicin hydrochloride injection sites that showed no signs of resolution during a 4-week recovery period.

Hemolytic Potential

The hemolytic potential of CAELYX® and STEALTH® placebo liposomes in human blood was assessed *in vitro*, as well as their compatibility with human serum and plasma. Neither CAELYX® 1.0 mg/mL nor empty STEALTH® liposomes induced hemolysis of human erythrocytes, nor did either cause coagulation or precipitation of human serum or plasma.

Lysophosphatidylcholine (LPC) is a degradation product of the phosphatidylcholine component of the liposomes. An additional hemolytic potential study using CAELYX® formulations prepared with 0 mg/mL, 0.5 mg/mL, or 0.88 mg/mL LPC caused no hemolysis of rat blood cells.

Dermal Lesion Development

The effect of peak dosage and dose frequency on dermal lesion development and myelosuppression was studied in dogs. CAELYX® 0.5, 1.0, 1.5 mg/kg was administered q7d, q14d, or q28d by intravenous (cephalic) catheter for 6-12 weeks. The higher dose intensities with lower dose frequency (1.0 mg/kg q14d and 1.5 mg/kg q28d) produced minimal evidence of cyclic depression of hemoglobin and hematocrit. In both groups, the hemoglobin and hematocrit values recovered to prestudy values at the end of the study. The onset of lesions occurred within 1 to 2 weeks after initiation of treatment and began to heal at rates that varied depending on lesion severity and dose frequency**.**

Myelosuppression was mild with all treatment regimens and no evidence of treatment-related leukopenia was observed. Dosages of 0.5 mg/kg given every 2 or 4 weeks were tolerated much better than the weekly doses at 0.5 mg/kg. Comparison of groups that received 0.5 mg/kg/treatment showed clear dose frequency-related effects on lesion development, lesion severity, and general toxicity. Integration of current results with previous studies showed a similar frequency-dependent effect with 1.0 mg/kg; weekly and every 2-week regimens produced severe toxicity while a 3-week dose cycle was better tolerated.

Cardiotoxicity

Cardiotoxicity is frequently observed in animals and man administered non-liposomal doxorubicin. However, in studies with CAELYX® in rats and dogs it was observed that cardiotoxicity was either absent or present at a substantially decreased incidence and severity. A multiple-dose study was carried out to evaluate the relative cardiotoxicity of CAELYX® and doxorubicin hydrochloride administered to male rabbits by intravenous injection q5d for targeted cumulative dosages of 14 or 21 mg/kg. Treatment was interrupted twice for 26 days to allow recovery from short-term toxicities unrelated to cardiotoxicity. Necropsies were conducted 1, 5, and 13 weeks after the 14th dose and 13 weeks after the 21st dose; hearts were examined for histopathological changes at each point. Lesion severity and incidence at five sites within the heart were also utilized to calculate a cardiotoxicity score for each animal.

Nine early deaths occurred in the CAELYX® group, 3 due to cardiotoxicity and 5 due to generalized stress secondary to dermal lesions; 5 early deaths occurred in the doxorubicin hydrochloride group, all with evidence of cardiotoxicity. Cardiac lesions were more severe and frequent in the doxorubicin hydrochloride group: overall, 4/25 (16%) CAELYX®-treated

animals with cardiotoxicity compared to 10/15 (67%) doxorubicin hydrochloride-treated animals. The decreased cardiotoxicity was not due to increased latency of the lesion; there was no significant increase in lesion incidence or severity with time post-treatment. Cardiomyopathy increased in evidence and severity with time after treatment in the doxorubicin hydrochloride treatment group. Up to 50% more CAELYX® (21 mg/kg cumulative dose) could be given without incurring increased cardiotoxicity compared to doxorubicin hydrochloride (14 mg/kg cumulative dose).

STEALTH® Liposome Placebo

In addition to the mutagenicity and developmental studies, and the acute and long-term studies in which placebo liposomes were used as controls, STEALTH® Liposome Placebo was evaluated for its potential to induce cardiovascular changes in dogs and neurobehavioral changes in rats. In the cardiovascular study, dogs showed a significant decrease in blood pressure (19-70%) immediately after the start of dosing followed by a rapid partial recovery after the end of dosing, and a return to normal values within 4-6 hours post-dose. Compensating acceleration in heart rate was not seen. The dose rate did not affect the extent of hypotension, but inversely affected the duration. In the rat study, placebo liposomes did not induce any adverse neurobehavioral effects or evidence of neurotoxicity.

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PART III: CONSUMER INFORMATION

CAELYX®

Pegylated Liposomal Doxorubicin Hydrochloride for Injection

This leaflet is part III of a three-part "Product Monograph" published when CAELYX® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CAELYX®. Contact your doctor or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you start using this medicine. Keep this leaflet. You may need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:

- Patients with metastatic breast cancer who are at risk for heart problems associated with conventional doxorubicin;
- Patients with advanced ovarian cancer who have not been successfully treated with standard first-line chemotherapy;
- Patient with AIDS-related Kaposi's sarcoma who have a low number of a specific type of white blood cell (CD4 lymphocytes) and extensive skin and mucous membrane or internal organ disease which has progressed despite therapy or who are intolerant to prior systemic combination chemotherapy.

What it does:

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

When it should not be used:

- If you are hypersensitive (allergic) to doxorubicin hydrochloride or any of the other ingredients of CAELYX®.
- If you are breast-feeding. Because doxorubicin hydrochloride may be harmful to nursing infants, women must discontinue breast-feeding before starting treatment with CAELYX®. Health experts recommend that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV
- If you think you are pregnant, because the active ingredient doxorubicin hydrochloride in CAELYX® may cause birth defects. Avoid becoming pregnant while you or your partner are receiving CAELYX® and in the six months following discontinuation of CAELYX® treatment.

What the medicinal ingredient is:

CAELYX® is pegylated liposomal doxorubicin hydrochloride. The active substance is doxorubicin hydrochloride in a pegylated liposomal formulation in a 2 mg/mL concentrate suspension for infusion.

What the important nonmedicinal ingredients are:

The STEALTH® liposome carriers are composed of N-(carbamoyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains approximately 2 mg of ammonium sulfate; 1.55 mg of histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control and 94 mg of sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the STEALTH® liposomes.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

CAELYX® should be prescribed and managed by healthcare professional specialized in the use of cancer drugs.

Possible serious side effects with the use of CAELYX® include:

- Heart damage, including congestive heart failure and weakening of heart muscle;
- Acute infusion reaction;
- Decrease of blood cell production (myelosuppression);
- Secondary oral cancer including fatal cases.

BEFORE you use CAELYX® talk to your doctor or pharmacist:

- If you have any of the following conditions. The dose of CAELYX® may need to be adjusted:
  - Previous treatment with anthracyclines (doxorubicin, epirubicin, etc.);
  - Chest radiation;
  - Heart and blood vessel problems;
  - Liver problems or disease;
- If you are diabetic, because CAELYX® contains sugar which may require an adjustment to the treatment of your diabetes.
- If you have a history of myelosuppression;
- If you think you are pregnant or are breast-feeding.

INTERACTIONS WITH THIS MEDICATION

Please inform your doctor and pharmacist:

- If you are taking or have recently taken any other medicines, even those not prescribed
- About any other cancer treatments, you are on or have been taking, as particular care needs to be taken with treatments which reduce the number of white blood cells. If you are unsure about what treatments you have received or any illnesses you have had, discuss these with your doctor.

PROPER USE OF THIS MEDICATION

Usual dose:

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

If you are being treated for breast or ovarian cancer, CAELYX® will be administered at a dose of 50 mg per square meter of your body surface area (based on your height and weight). The dose is

repeated every 4 weeks for as long as the disease does not progress, and you are able to tolerate the treatment.

If you are being treated for Kaposi's sarcoma, CAELYX® will be administered at a dose of 20 mg per square metre of your body surface area (based on your height and weight). The dose is repeated every 2 to 3 weeks.

Overdose:
If You Receive More CAELYX® Than You Should:

Acute overdosing worsens side effects like sores in the mouth or decrease in the number of white blood cells and platelets in the blood. Treatment will include administration of antibiotics, platelet transfusions, use of factors which stimulate production of white blood cells and symptomatic treatment of mouth sores.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Do not drive or operate any tools or machines if you feel tired or sleepy from treatment with CAELYX®.
During the infusion of CAELYX®, the following reactions may occur: flushing of the face, shortness of breath, headache, chills, back pain, tightness in the chest and/or throat, low or high blood pressure and puffing of the face. In very rare cases, seizures (convulsions) have occurred. Stinging or swelling of the skin at the site of injection may also occur. If the drip stings or hurts while you are receiving a dose of CAELYX®, tell your doctor immediately.

Opportunistic infections are otherwise rare infections that typically do not occur in healthy people and develop because the immune system is weak. The commonly reported opportunistic infections during CAELYX® treatment include fungal (candidiasis), cytomegalovirus (CMV*), Pneumocystis carinii* pneumonia (PCP), and *Mycobacterium avium* complex (MAC) infections.

Between infusions, the following may occur:

- Decrease in the number of white blood cells, which can increase the chances of infections. Anemia (reduction in red blood cells) may cause tiredness, and decreased platelets in the blood may increase the risk of bleeding. In rare cases, having low white blood cells may lead to severe infection.
- Change in liver function;
- Stomach pains/sickness (nausea or vomiting), diarrhea, constipation, pain or sores in mouth, oral thrush (a fungal infection in the mouth), sores in nose, bleeding from your nose, cold sores, loss of appetite, weight loss and tongue inflammation;
- General feeling of tiredness, sleepiness, confusion, dizziness, weakness, bone pain, breast pain, muscle pain, leg cramps or swelling, general swelling, inflammation of the retina, tearing of the eye, blurred vision, feeling of pins and needles or pain in hands and feet;
- Hair loss, inflammation of hair follicles, scaly skin, inflammation or eruption of skin, abnormal skin pigmentation, nail disorder, rash, redness, swelling and sores on the palms of your hands and feet (hand-foot syndrome - see below);
- Heart problems, e.g., irregular heartbeat, weakening of the heart muscle;
- Fever, increased temperature or any other sign of infection which may be related to your disease;
- Respiratory problems, i.e., coughing or difficulty in breathing, which may be linked to infections you have caught as a result of your disease;
- If you have previously had skin reactions, i.e., pain, redness and dryness of skin, during treatment with radiotherapy, this may also happen with CAELYX®.

Contact your doctor immediately if:

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

Strategies to Prevent and Treat Hand-Foot Syndrome

- Soak hands and/or feet in basins of cold water when possible (e.g., while watching television, reading, or listening to the radio);
- Keep hands and feet uncovered (no gloves, socks, etc.);
- Stay in cool places (under tree shade, by a swimming area with shade etc.);
- Take cool baths or stay in the water during the summer;
- Avoid vigorous exercise that might cause trauma to the feet (e.g. jogging);
- Avoid exposure of skin to very hot water (e.g., jacuzzis, saunas);
- Avoid tight-fitting footwear or high-heeled shoes.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Allergic-like reactions (during infusion) such as flushing of the face, shortness of breath, headache, chills, tightness in the chest and/or throat, low or high blood pressure and possibly dizziness and puffing of the face, stinging or swelling of the skin at the site of injection;		✓	
	If the drip stings or hurts while you are receiving a dose of CAELYX®;		✓	
	Reddening painful skin on your hands and feet;		✓	
	Heart problems such as irregular heartbeat, shortness of breath and/or swelling of feet or hands;		✓	
	Fever or any other sign of an infection, bruising more easily than normal, signs of anemia such as tiredness, being short of breath, and looking pale;		✓	
	Mouth sores.		✓	
Uncommon	Swelling, warmth, or tenderness in the soft tissues of your leg, sometimes with pain which gets worse when you stand or walk;		✓	
	Sudden shortness of breath or sharp chest pain that may worsen with deep breathing or coughing.		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rarely	Convulsion during infusion reactions;		✓	
	Painful reddening of the skin and or blister on the body or mouth.		✓	
Reported from post-marketing with unknown frequency	Oral cancer may occur during or following treatment with CAELYX®. Mouth discolouration, discomfort, sores or ulcerations should be reported to your doctor.		✓	

This is not a complete list of side effects. For any unexpected effects while taking CAELYX®, contact your doctor or pharmacist.

HOW TO STORE IT

Keep CAELYX® out of reach and sight of children.

Do not use if CAELYX® solution is discolored or shows evidence of precipitation or particles.

CAELYX® should be stored in the refrigerator (2ºC – 8ºC). Do not freeze. Discard partially used vials.

Diluted CAELYX® should be refrigerated and used within 24 hours.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at:

- https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

- Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html).

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.janssen.com/canada
or by contacting the sponsor, Janssen Inc.
at: 1-800-567-3331and 1-800-387-8781

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